



HAL
open science

A role for antibodies in natural HIV control

Arnaud Moris, Mathias Pereira, Lisa Chakrabarti

► **To cite this version:**

Arnaud Moris, Mathias Pereira, Lisa Chakrabarti. A role for antibodies in natural HIV control. *Current Opinion in HIV and AIDS*, 2019, 14 (4), pp.265-272. 10.1097/COH.0000000000000554. hal-02172944

HAL Id: hal-02172944

<https://hal.science/hal-02172944>

Submitted on 4 Jul 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - ShareAlike 4.0 International License

A Role for Antibodies in Natural HIV Control

Arnaud Moris^{1,2*}, Mathias Pereira¹ and Lisa Chakrabarti^{3*}

Author affiliations:

¹ Sorbonne Université, INSERM, CNRS, Center for Immunology and Microbial Infections – CIMI-Paris, Paris, France

² Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Université Paris-Sud, Université Paris-Saclay, Gif-sur-Yvette, France

³ Virus and Immunity Unit, Control of Chronic Viral Infections (CIVIC) Group, Institut Pasteur, Paris, France

A.M. and L.A.C. contributed equally to this work

* Correspondence:

Arnaud Moris (arnaud.moris@i2bc.paris-saclay.fr) and Lisa A. Chakrabarti (chakra@pasteur.fr).

Arnaud Moris, Center for Immunology and Microbial Infections – CIMI-Paris, 91 Bd de l'Hôpital, 75013 Paris, France.

Lisa Chakrabarti, Virus and Immunity Unit, Control of Chronic Viral Infections (CIVIC) group, Institut Pasteur, 28 rue du Dr Roux, 75724 Paris Cedex 15, France

27 **Abstract (198 words)**

28

29 **Purpose of the review**

30 Rare patients naturally control HIV replication without antiretroviral therapy. Understanding
31 the mechanisms implicated in natural HIV control will inform the development of
32 immunotherapies against HIV. Elite controllers (EC) are known for developing efficient
33 antiviral T cell responses, but recent findings suggest that antibody (Ab) responses also play a
34 significant role in HIV control. We review the key studies that uncovered a potent memory B
35 cell response and highly functional anti-HIV Ab in EC, and explore the mechanisms that may
36 account for the distinct properties of their humoral response.

37

38 **Recent findings**

39 EC maintain a large HIV-specific memory B cell pool that is sustained by efficient Tfh
40 function. Neutralizing Ab rarely show high titers in controllers, but seem capable, at least in
41 certain cases, of neutralizing contemporaneous viral strains. In addition, EC display a unique
42 HIV-specific Ab profile in terms of isotype, antigen specificity, and glycosylation pattern,
43 resulting in polyfunctional Ab effector functions that may promote infected cell lysis and
44 prime effectors of the antiviral immune response.

45

46 **Summary**

47 Lessons from EC studies argue for the importance of integrating the many parameters
48 defining a polyfunctional Ab response when evaluating candidate vaccines and
49 immunotherapeutic approaches directed at HIV.

50

51 **Key words:** HIV control, memory B cells, neutralizing antibodies, ADCC, CD4+ T cell help.

52

53

54

55

56

57

58 INTRODUCTION

59

60 Different groups of HIV-infected individuals naturally control HIV-1 (HIV) replication in the
61 absence of combined antiretroviral therapy (cART): elite controllers (EC), who represent
62 fewer than 1% of HIV-infected individuals and maintain very low to undetectable viremia
63 (generally <50 copies HIV RNA/mL); viremic controllers (VC), who show partial viral
64 control; and post-treatment controllers, who received cART but did not resume viral
65 replication after treatment interruption [1,2]. Importantly, these groups of patients show a
66 very low risk of progression to AIDS and usually maintain high CD4+ T cell counts [3]. In
67 particular, EC show the strongest protection from disease and provide a unique opportunity to
68 study immune responses involved in natural viral suppression [4].

69

70 It was long thought that cytotoxic CD8+ T cells (CTL) were the unique players involved in
71 natural HIV control. Indeed, a fraction of EC exhibit potent CTL responses against HIV-
72 infected cells, often associated with the expression of protective HLA alleles such as HLA-
73 B*57 and B*27 [2]. However, a growing body of evidence suggests that the humoral
74 response, sustained by efficient CD4+ T cell help, is also a key player in HIV control. In this
75 review, we highlight the recent works that uncovered a potent memory B cell response in EC,
76 and that demonstrated the capacity of EC's sera to perform multiple effector functions
77 possibly involved in HIV control. We also examine the mechanisms that could underlie the
78 development and persistence of HIV-specific memory B cells in EC, including the
79 preservation of CD4+ T follicular helper (Tfh) cell functions and the possibility of more
80 efficient antigen presentation.

81

82 **Low Neutralizing antibody titers in EC**

83 The role of the humoral response was initially neglected in the HIV control research field, as
84 several studies had shown that EC had low HIV neutralizing antibody (NAb) titers as
85 compared to viremic individuals [5-9]. In addition, EC with the lowest levels of HIV
86 replication, who remained undetectable even in high-sensitivity viral loads assays (≤ 1 copy
87 HIV RNA/mL), showed signs of low-intensity antibody responses, with fewer viral protein
88 bands on HIV western blots, lower NAb titers, and lower cross-neutralization breadth [10].
89 Conversely, in viremic patients, the breadth of neutralization has been associated with higher
90 viral loads [8,9,11-15], longer duration of viral exposure, and higher viral diversity [16]. In

91 other words, in EC as in viremic patients, the availability of viral antigens seems to determine
92 the magnitude of the antibody response, as well as its cross-neutralization capacity.

93
94 It should be noted, however, that EC show a marked heterogeneity, with some presenting
95 broad cross-neutralization capacity while others show minimal or no neutralization [5-8,17].
96 A flurry of broadly neutralizing antibodies (bNAbs) capable of neutralizing diverse HIV
97 strains were identified during the past decade. Of note, some of the original bNAbs were
98 cloned from HIV-specific memory B cells isolated from EC, indicating that these rare patients
99 have the capacity to produce potent anti-HIV antibodies [17,18].

100

101 **Preserved memory B cell differentiation in EC**

102 Memory B cells, which are essential to sustain humoral immunity in the long-term, can be
103 divided in 4 subpopulations: activated memory (AM), resting memory (RM), intermediate
104 memory (IM) and tissue-like memory (TLM) B cells [19]. AM and TLM B cells, with the
105 latter showing signs of anergy, are associated with higher levels of viremia [20,21]. In
106 contrast, RM cells, which contribute to the long-term persistence of humoral responses, are
107 decreased in progressor patients [19,22]. The picture that emerges is that of an abnormal
108 immune activation that drives memory B cell exhaustion. cART decreases TLM and AM B
109 cell proportions to near-normal levels in HIV-infected patients, but only restores the RM
110 compartment in a subset of patients [20,23,24]. In EC, the proportions of the four memory B
111 cell subsets are generally comparable to those observed in HIV-negative individuals [20,25].
112 However, the proportions of TLM B cells remain slightly elevated in EC, suggesting a degree
113 of ongoing immune activation even in well-controlled HIV infection [20,25].

114

115 **Potent HIV-specific memory B cell responses in EC**

116 A key difference between EC and treated patients is that EC maintain a high frequency of
117 HIV-specific memory B cells despite their low viral loads. These findings were obtained by
118 measuring the frequency of circulating memory B cells capable of binding gp140 fluorescent
119 probes [26] and by performing B cell ELISPOT assays [25]. Viremic patients who initiate
120 cART show a marked decrease in the frequency of HIV-specific antibody-secreting cells
121 (ASC), and patients treated in the long-term show low or undetectable HIV-specific ASC,
122 consistent with the notion that viral replication is needed to constantly drive plasmablast
123 differentiation in these patients [26-29]. In contrast, EC maintain a sizable memory B cell
124 compartment despite limited antigenemia, suggesting that HIV-specific memory B cells are

125 either longer lived in these rare patients or still generated or renewed due to antigen/Tfh
126 access in lymphoid structures even with very low blood antigenemia.

127

128 This is not to say that EC are free of HIV replication. EC are more and more often treated
129 with cART, which decreases immune activation, slightly increases CD4⁺ T cell counts,
130 decreases ASC frequency, and further decreases the viral load in these already well-controlled
131 patients [26,30,31]. Simian models suggest that limited viral replication persists in the
132 germinal centers (GC) of lymphoid organs in untreated controller monkeys [32]. It is thus
133 conceivable that the persistence of HIV-specific memory B cells in EC depends on residual
134 viral replication in GC, at the very site of antibody response maturation. Interestingly,
135 residual HIV replication appears to drive a persisting low-grade inflammation in some EC and
136 to influence B cell fates. A specific inflammation profile, characterized by increased levels of
137 CXCL13, sCD40L, IP10, RANTES, and TNF α in plasma, has been associated with the
138 capacity to develop cross-neutralizing antibody responses in EC [33]. Further studies
139 confirmed the association between CXCL13 levels and the breadth of the neutralizing Ab
140 response in EC, emphasizing the role of this chemokine in Ab maturation [34].

141

142 **Association between memory B cells responses and HIV neutralization capacity**

143 Several studies analyzed whether the persistence of HIV-specific ASC, which include
144 plasmablasts and memory B cells, might correlate with the titers of HIV-specific Ab and/or
145 the breadth of neutralization. Most studies carried out on heterogeneous cohorts of EC failed
146 to observe a correlation between cellular B cell responses and the magnitude or neutralization
147 capacity of the Ab response [13,28,35]. Interestingly, by dividing EC into two subgroups
148 expressing or not the protective HLA-B*57 allele, we observed among HLA-B*57⁺ EC that
149 the frequency of HIV-specific ASC correlated positively with the capacity to neutralize
150 various HIV strains, including Transmitter/Founder viruses [25]. As EC show an early
151 spontaneous control of HIV replication [36], which is probably mediated by CTL antiviral
152 effect in HLA-B*57⁺ EC [37], we propose that these CTL responses might favor the
153 establishment of efficient memory B cell responses with cross-neutralization capacity,
154 through the rapid control of the viral load, which could in turn avoid B cell exhaustion and
155 preserve Tfh function.

156

157

158

159 **A role for autologous virus neutralization in HIV control?**

160 HIV constantly evades the selective pressure imposed by NAb through mutational escape, so
161 that at a given time the patient serum can neutralize previous but not contemporaneous viral
162 strains isolated from the same patient [38]. Intriguingly, significant levels of autologous NAb
163 (that is, capable of neutralizing the contemporaneous viral strains) were detected in viremic
164 controllers [39]. Recently, an in-depth longitudinal characterization of the humoral response
165 in a HLA-B*57+ viremic controller revealed that this patient harbored autologous NAb
166 capable of neutralizing 88.5% of its circulating viral clones, suggesting that these NAb
167 contributed to HIV control [40]. Interestingly, NAb in this patient could also cross-neutralize
168 diverse heterologous HIV strains, suggesting that in some cases viral diversification can be
169 efficiently matched by a diversification of the NAb response.

170

171 **Preserved Tfh function may underlie the persistence of potent memory B cell responses**
172 **in HIV controllers**

173 Tfh cells, which reside within GC, provide help to B cells in the form of costimulatory signals
174 and secretion of cytokines. Chronic HIV infection perturbs Tfh function, but paradoxically
175 leads to an increase in Tfh numbers, which contributes to GC hyperplasia and
176 lymphadenopathy [41]. Circulating Tfh (cTfh), defined as blood CXCR5+ CD4+ T cells, are
177 thought to represent a form of memory Tfh, that can reacquire B cell helper functions upon
178 antigenic stimulation [42,43]. Interestingly, an increased proportion of cTfh subsets that
179 express PD-1 [44] or PD-1 in the absence of CXCR3 [45,46] was associated with the
180 development of a broad HIV-neutralizing antibody response, in adults and children. This
181 suggests that Tfh that experience ongoing antigenic stimulation, as measured by PD-1
182 expression, are needed to sustain continued antibody maturation in the context of chronic HIV
183 infection.

184

185 HIV control is associated with the persistence of highly functional CD4 effectors endowed
186 with polyfunctional cytokine secretion and cytotoxic capacities [47,48]. The expression of
187 HIV-specific T cell receptors of particularly high affinity accounts for the persistence of CD4
188 effector responses in EC [49,50]. Recent studies indicate that Tfh function is also highly
189 efficient in EC. The frequency of HIV-specific cTfh, as measured by MHC-II tetramer
190 labeling, remains higher in EC than in treated patients, and correlates with a higher production
191 of HIV-specific antibodies in memory B cells/cTfh cocultures [51]. In addition, HIV-specific
192 Tfh defined functionally as CXCR5+ CD4+ T cells with IL-21 secretion capacity are also

193 preserved in EC, and show an association with the frequency of Env-specific memory B cells
194 [52]. Thus, key Tfh/B cell interactions are preserved in controlled HIV infection, which
195 enables continued antibody affinity maturation (see Graff-Dubois *et al.* in this issue). These
196 findings emphasize the need to induce robust Tfh function in vaccination and immune
197 restoration strategies targeting HIV.

198

199 **A bias in Ab isotype and specificity in EC**

200 In addition to pathogen neutralization, Abs accomplish a variety of effector functions, with Fc
201 receptors (FcR) binding leading to cytokine secretion, antibody-dependent cellular
202 phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC), and
203 activation of the complement cascade. These different functions are strongly influenced by
204 the immunoglobulin (Ig) isotype and the glycosylation status of the Ig Fc regions [53].

205

206 Although the IgG1 subclass dominates HIV-specific responses, the proportion of IgG isotypes
207 varies depending on HLA type and clinical parameters [54-57]. A sequential study of Env-
208 specific antibodies in controller and progressor patients showed that isotype profiles evolved
209 over time, with a more prevalent Env-specific IgG2 response in controllers at early time
210 points, while the IgG2 response developed more slowly in progressors [58]. In contrast, Env-
211 specific IgG3 were present in both groups at early time points, but were progressively lost in
212 progressors [58]. Isotype variations likely impact Fc-dependent functions, as for instance
213 IgG1 and IgG3 generally bind Fc γ Rs with higher affinity than IgG2 and IgG4, with IgG3
214 being particularly efficient at mediating HIV internalization [59]. It is relevant that the loss of
215 HIV-specific IgG3 occurs in synchrony with the loss of Fc-mediated functions that have been
216 associated with viral control (see below) [60]. Accordingly, the sera from EC exhibiting
217 strong polyfunctional antiviral activities are enriched in Abs of IgG1 and IgG3 subclasses
218 [56]. Taken together, these studies suggest that the persistence of Env-specific IgG able to
219 bind Fc γ Rs with high affinities could play a role in viral control.

220

221 Interestingly, HIV-specific IgA Abs were also detected at higher frequency in the sera of EC
222 than in those of treated and viremic patients [61]. IgA responses in EC displayed broader
223 antigen specificities and a particularly high avidity to the gp41 antigen [61]. Although serum
224 IgA can clearly induce FcR-mediated phagocytosis of HIV [62], their phagocytic capacity
225 appears reduced as compared to IgG1 and IgG3 [59]. However, IgA can engage Fc α RI to

226 trigger ADCC by monocytes and neutrophils, and IgG1 and IgA may actually cooperate
227 rather than compete in the induction of FcR-mediated effector functions [63].

228

229 A role of Gag-specific antibodies in viral control has also been proposed. It is interesting that
230 Gag-specific IgG2 [64,65] and IgG1 [66,67] have been associated with long-term
231 nonprogression. Gag-specific IgG2 Abs seem particularly abundant in HLA-B*57-negative
232 EC, and may reflect a role for the humoral response in viral control when the CD8 response is
233 not dominant [57,68]. However, the significance of anti-Gag responses in HIV infection
234 remains unclear, as Gag proteins are not expressed at the cell or virion surface, and should
235 thus not be accessible to Abs. Gag-specific Abs may still be able to capture secreted Gag,
236 broken virions, or infected cell fragments, which may in turn facilitate the uptake and
237 presentation of Gag antigens to Gag-specific CD4+ and CD8+ T cells, which are
238 immunodominant in EC and thought to play a key role in suppressing HIV replication [2,69].

239

240 **A more potent ADCC function in EC?**

241 HIV-specific ADCC, primarily mediated by NK cells, develops rapidly in the course of HIV
242 infection and exerts an immune selective pressure on the virus, suggesting that it contributes
243 to decrease the pool of infected cells during the early stages of infection [70-72]. Whether
244 ADCC participates in viral control in EC during the chronic stage of infection remains
245 debated [73]. Several studies did not detect an improved capacity of EC sera to mediate
246 ADCC [56,74,75]. In contrast, Abs mediating ADCC were found to be increased in other EC
247 cohorts [5,76], with one study reporting a predominant ADCC response in HLA-B*57-
248 negative EC, as compared to HLA-B*57-positive EC [77].

249

250 These contrasting findings reflect the heterogeneity of ADCC responses in EC, but also the
251 variable definitions of controller status in the different EC cohorts. The choice of the control
252 group may also influence study outcome, as for instance viremic patients at an advanced stage
253 of infection tend to show lower HIV-specific Ab levels in the circulation. There is clear
254 evidence that the level of Env-specific Ab binding at the surface of infected cells is a correlate
255 of ADCC activity [75]. Indeed, NAbs with an intrinsically higher capacity to bind the surface
256 of infected CD4+ T cells show more efficient ADCC activity against these cells [78].
257 Competition between different types of antibodies may also influence ADCC function [79].
258 IgG3 are likely important in NK-mediated ADCC, as they have a particularly high affinity for
259 FcγRIIIA, which is the only FcR expressed at the surface of NK cells in 80% of humans [80].

260

261 ADCC activity also depends on the strength of NK cell activation. Specific associations
262 between certain NK cell receptors allotypes and their MHC-I molecule ligands, such as
263 KIR3DL1 and HLA-B*57, influence disease progression and are associated with lower
264 viremia [81]. Nonetheless, NK cells from EC and progressors have so far shown similar
265 capacities to perform ADCC [56,74,82]. Therefore, the involvement of NK receptor allotypes
266 in viral control may rely on the direct recognition of infected cells by NK cells, through NK
267 receptor engagement rather than ADCC.

268

269 **Polyfunctional Ab-effector functions in EC**

270 Given the diversity of Ab effector functions, it seems unlikely that a single attribute of the Ab
271 response may account for the unique capacity of EC to control HIV infection. To tackle this
272 issue, Ackerman and Alter developed a systematic approach to study in a single sample an
273 array of functions, including ADCC, NK activation, complement deposition (ADCD), ADCP,
274 and Ab attributes, such as glycosylation status and FcR binding capacity [56,66]. This
275 "systems serology" approach did not show a superior capacity of EC's sera to perform any of
276 the above-mentioned functions. Rather, it revealed that the different Ab functions, except for
277 ADCP, strongly correlated with one another in EC. In particular, ADCD correlated with all
278 other functions, suggesting that EC developed a more coordinated Ab response than other
279 patient groups [56]. EC exhibiting these polyfunctional antiviral activities had sera enriched
280 in IgG1 and IgG3 HIV-specific Abs, pointing out to the importance of isotype subclasses in
281 determining the overall quality of the antibody response [56].

282

283 Ab effector functions depend on binding to FcRs and to initiators of the complement cascade,
284 with these steps being tightly regulated by the glycosylation of the Ig Fc region [83,84]. In
285 humans, the IgG Fc-domain harbors a single glycosylation site that can accommodate up to
286 30 documented different glycan structures. In EC, a shift of the glycosylation profile toward
287 agalactosylated glycoforms was observed in the total Ab pool [85]. In particular, HIV-specific
288 Abs exhibited a high frequency of agalactosylated, afucosylated, and asialylated glycans [85].
289 These particular Ab glycoforms have been associated with enhanced FcR-mediated antiviral
290 functions, and may thus account for the quality of Ab effector functions in EC. Interestingly,
291 in EC, the presence of the particular glycoform G1S1F was strongly associated with
292 emergence of HIV-specific IgG3, suggesting that coordinated changes underlie the
293 development of polyfunctional Ab responses [66]. Overall, systems serology studies are

294 starting to shed light on the many interdependent parameters involved in defining the quality
295 of antiviral Ab responses.

296

297 In addition to mediating direct antiviral activities, FcR-dependent Ab functions such as ADCP
298 and complement deposition also enhance innate and adaptive immunity, by inducing cytokine
299 secretion and promoting viral antigen presentation. For instance, injection of bNAbs in SHIV
300 infected macaques and HIV-infected patients was shown to enhance T cell immunity and
301 increase the neutralization breadth of endogenous Abs [86,87]. CD8+ T cell responses in
302 particular were shown to contribute to durable viral control in bNAb-treated animals [88]. The
303 underlying mechanisms are not elucidated yet, but may depend on increased formation of
304 immune complexes and/or complement opsonisation (see Naranjo-Gomez & Pelegrin in this
305 issue). Viral immune complexes were shown to promote antigen capture and dendritic cell
306 (DC) maturation [89,90]. HIV immune complexes could also induce an antiviral state by
307 triggering the production of type I interferon by plasmacytoid DC [91]. The enhancing effect
308 of NAbs on adaptive antiviral immunity has yet to be fully investigated in EC, but it is
309 interesting to note that DC from EC are more efficient at capturing HIV particles [92].

310

311 **CONCLUSION**

312 Increasing evidence suggest that humoral responses play an important role in natural HIV
313 control. EC maintain a large HIV-specific memory B cell pool that is sustained by efficient
314 Tfh function. NAb rarely show high titers in controllers, but seem capable, at least in certain
315 cases, of neutralizing contemporaneous viral strains, and thus of directly contributing to viral
316 control. In addition, EC display a unique HIV-specific Ab profile in terms of isotype and
317 glycosylation pattern, resulting in polyfunctional Ab effector functions that may promote
318 infected cell lysis and prime multiple effectors of the antiviral immune response. Lessons
319 from EC studies argue for the importance of integrating the many parameters defining a
320 polyfunctional Ab response when evaluating candidate vaccines and immunotherapeutic
321 approaches directed at HIV.

322

323 **KEY POINTS**

- 324 - Persistence of a large HIV-specific memory B cell pool in EC
- 325 - Efficient Tfh help sustains memory B cells in EC
- 326 - Efficient neutralization of contemporaneous autologous viral strains in some EC and VC
- 327 - Increased frequency of Gag-specific antibodies in EC

- 328 - Persistence of Env-specific IgG3, which mediate NK-dependent ADCC in EC
329 - Shift of the HIV-specific IgG glycosylation profile in EC
330 - Polyfunctional Ab effector responses in EC
331 - Converging evidence that the humoral response plays a key role in natural HIV control
332
333

334 **ACKNOWLEDGMENTS**

335 We thank all the participants and investigators of the ANRS CO21 CODEX cohort. We
336 apologize to the authors whose valuable work could not be discussed due to length
337 constraints.
338

339 **FINANCIAL SUPPORT and SPONSORSHIP**

340 We thank ANRS, Sidaction, and ANR for financial support.
341

342 **CONFLICTS OF INTEREST**

343 The authors declare no conflict of interest.
344

345 **REFERENCES**

- 346 1. Lambotte O, Delfraissy J-F: **HIV controllers: a homogeneous group of HIV-1 infected patients with a spontaneous**
347 **control of viral replication.** *Clinical Infectious Diseases* 2005, **41**:1053-1056.
348 2. Saez-Cirion A, Manel N: **Immune Responses to Retroviruses.** *Annu Rev Immunol* 2018, **36**:193-220.
349 3. Grabar S, Selinger-Leneman H, Abgrall S, Pialoux G, Weiss L, Costagliola D: **Prevalence and comparative**
350 **characteristics of long-term nonprogressors and HIV controller patients in the French Hospital Database on**
351 **HIV.** *AIDS* 2009, **23**:1163-1169.
352 4. Walker BD, Yu XG: **Unravelling the mechanisms of durable control of HIV-1.** *Nat Rev Immunol* 2013, **13**:487-498.
353 5. Lambotte O, Ferrari G, Moog C, Yates NL, Liao H-X, Parks RJ, Hicks CB, Owzar K, Tomaras GD, Montefiori DC, et al.:
354 **Heterogeneous neutralizing antibody and antibody-dependent cell cytotoxicity responses in HIV-1 elite**
355 **controllers.** *AIDS (London, England)* 2009, **23**:897-906.
356 6. Pereyra F, Addo MM, Kaufmann DE, Liu Y, Miura T, Rathod A, Baker B, Trocha A, Rosenberg R, Mackey E, et al.:
357 **Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy.**
358 *The Journal of infectious diseases* 2008, **197**:563-571.
359 7. Bailey JR, Lassen KG, Yang HC, Quinn TC, Ray SC, Blankson JN, Siliciano RF: **Neutralizing antibodies do not**
360 **mediate suppression of human immunodeficiency virus type 1 in elite suppressors or selection of plasma**
361 **virus variants in patients on highly active antiretroviral therapy.** *J Virol* 2006, **80**:4758-4770.
362 8. Sajadi MM, Guan Y, DeVico AL, Seaman MS, Hossain M, Lewis GK, Redfield RR: **Correlation between circulating**
363 **HIV-1 RNA and broad HIV-1 neutralizing antibody activity.** *J Acquir Immune Defic Syndr* 2011, **57**:9-15.
364 9. Doria-Rose NA, Klein RM, Daniels MG, O'Dell S, Nason M, Lapedes A, Bhattacharya T, Migueles SA, Wyatt RT,
365 Korber BT, et al.: **Breadth of human immunodeficiency virus-specific neutralizing activity in sera: clustering**
366 **analysis and association with clinical variables.** *J Virol* 2010, **84**:1631-1636.

- 367 10. Pereyra F, Palmer S, Miura T, Block BL, Wiegand A, Rothchild AC, Baker B, Rosenberg R, Cutrell E, Seaman MS, et
368 al.: **Persistent low-level viremia in HIV-1 elite controllers and relationship to immunologic parameters.** *The*
369 *Journal of infectious diseases* 2009, **200**:984-990.
- 370 11. Piantadosi A, Panteleeff D, Blish CA, Baeten JM, Jaoko W, McClelland RS, Overbaugh J: **Breadth of neutralizing**
371 **antibody response to human immunodeficiency virus type 1 is affected by factors early in infection but does**
372 **not influence disease progression.** *J Virol* 2009, **83**:10269-10274.
- 373 12. Deeks SG, Schweighardt B, Wrin T, Galovich J, Hoh R, Sinclair E, Hunt P, McCune JM, Martin JN, Petropoulos CJ, et
374 al.: **Neutralizing antibody responses against autologous and heterologous viruses in acute versus chronic**
375 **human immunodeficiency virus (HIV) infection: evidence for a constraint on the ability of HIV to**
376 **completely evade neutralizing antibody responses.** *J Virol* 2006, **80**:6155-6164.
- 377 13. Doria-Rose NA, Klein RM, Manion MM, O'Dell S, Phogat A, Chakrabarti B, Hallahan CW, Migueles SA, Wrammert J,
378 Ahmed R, et al.: **Frequency and phenotype of human immunodeficiency virus envelope-specific B cells from**
379 **patients with broadly cross-neutralizing antibodies.** *J Virol* 2009, **83**:188-199.
- 380 14. Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, Yu X, Wood B, Self S, Kalams S, et al.:
381 **Factors associated with the development of cross-reactive neutralizing antibodies during human**
382 **immunodeficiency virus type 1 infection.** *J Virol* 2009, **83**:757-769.
- 383 15. Rodriguez SK, Sarr AD, MacNeil A, Thakore-Meloni S, Gueye-Ndiaye A, Traore I, Dia MC, Mboup S, Kanki PJ:
384 **Comparison of heterologous neutralizing antibody responses of human immunodeficiency virus type 1 (HIV-**
385 **1)- and HIV-2-infected Senegalese patients: distinct patterns of breadth and magnitude distinguish HIV-1**
386 **and HIV-2 infections.** *J Virol* 2007, **81**:5331-5338.
- 387 16. Rusert P, Kouyos RD, Kadelka C, Ebner H, Schanz M, Huber M, Braun DL, Hoze N, Scherrer A, Magnus C, et al.:
388 **Determinants of HIV-1 broadly neutralizing antibody induction.** *Nat Med* 2016, **22**:1260-1267.
- 389 17. Scheid JF, Mouquet H, Feldhahn N, Seaman MS, Velinzon K, Pietzsch J, Ott RG, Anthony RM, Zebroski H, Hurley A,
390 et al.: **Broad diversity of neutralizing antibodies isolated from memory B cells in HIV-infected individuals.**
391 *Nature* 2009, **458**:636-640.
- 392 18. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, Oliveira TY, Pietzsch J, Fenyo D, Abadir A, Velinzon K, et al.:
393 **Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding.** *Science*
394 2011, **333**:1633-1637.
- 395 19. Moir S, Fauci AS: **B-cell responses to HIV infection.** *Immunol Rev* 2017, **275**:33-48.
- 396 20. Pensiero S, Galli L, Nozza S, Ruffin N, Castagna A, Tambussi G, Hejdeman B, Misciagna D, Riva A, Malnati M, et
397 al.: **B-cell subset alterations and correlated factors in HIV-1 infection.** *AIDS (London, England)* 2013, **27**:1209-
398 1217.
- 399 21. Kardava L, Moir S, Shah N, Wang W, Wilson R, Buckner CM, Santich BH, Kim LJY, Spurlin EE, Nelson AK, et al.:
400 **Abnormal B cell memory subsets dominate HIV-specific responses in infected individuals.** *The Journal of*
401 *clinical investigation* 2014, **124**:3252-3262.
- 402 22. Good KL, Avery DT, Tangye SG: **Resting Human Memory B Cells Are Intrinsically Programmed for Enhanced**
403 **Survival and Responsiveness to Diverse Stimuli Compared to Naive B Cells.** *The Journal of Immunology* 2009,
404 **182**:890-901.
- 405 23. Moir S, Ho J, Malaspina A, Wang W, DiPoto AC, O'Shea MA, Roby G, Kottlil S, Arthos J, Proschan MA, et al.:
406 **Evidence for HIV-associated B cell exhaustion in a dysfunctional memory B cell compartment in HIV-**
407 **infected viremic individuals.** *The Journal of experimental medicine* 2008, **205**:1797-1805.
- 408 24. Moir S, Buckner CM, Ho J, Wang W, Chen J, Waldner AJ, Posada JG, Kardava L, Shea MaO, Kottlil S, et al.: **B cells in**
409 **early and chronic HIV infection : evidence for preservation of immune function associated with early**
410 **initiation of antiretroviral therapy.** *Blood* 2010, **116**:5571-5579.

- 411 25. Rouers A, Klingler J, Su B, Samri A, Laumond G, Even S, Avettand-Fenoel V, Richetta C, Paul N, Boufassa F, et al.:
412 **HIV-Specific B Cell Frequency Correlates with Neutralization Breadth in Patients Naturally Controlling**
413 **HIV-Infection.** *EBioMedicine* 2017, **21**:158-169.
- 414 ** The analysis of ASC in a large cohort of EC revealed the persistence of HIV-specific
415 memory B cells in this group. A positive correlation between HIV-specific memory B cell
416 frequency and neutralization breadth was detected only in EC carrying the protective HLA-
417 B*57 allele.
- 418 26. Buckner CM, Kardava L, Zhang X, Gittens K, Justement JS, Kovacs C, McDermott AB, Li Y, Sajadi MM, Chun T-W, et
419 al.: **Maintenance of HIV-Specific Memory B-Cell Responses in Elite Controllers Despite Low Viral Burden.**
420 *Journal of Infectious Diseases* 2016:jiw163.
- 421 ** The detection of gp120-binding B cells in the circulation revealed that HIV-specific
422 memory B cells persisted at a high frequency in EC, while they were lost in treated patients.
- 423 27. Morris L, Binley JM, Clas BA, Bonhoeffer S, Astill TP, Kost R, Hurley A, Cao Y, Markowitz M, Ho DD, et al.: **HIV-1**
424 **antigen-specific and -nonspecific B cell responses are sensitive to combination antiretroviral therapy.** *J Exp*
425 *Med* 1998, **188**:233-245.
- 426 28. Bussmann BM, Reiche S, Bieniek B, Krznanic I, Ackermann F, Jassoy C: **Loss of HIV-specific memory B-cells as a**
427 **potential mechanism for the dysfunction of the humoral immune response against HIV.** *Virology* 2010, **397**:7-
428 13.
- 429 29. Fondere J-M, Huguet M-F, Macura-Biegun A, Baillat V, Ohayon V, Reynes J, Vendrell J-P: **Detection and**
430 **enumeration of circulating HIV-1-specific memory B cells in HIV-1-infected patients.** *Journal of acquired*
431 *immune deficiency syndromes (1999)* 2004, **35**:114-119.
- 432 30. Hatano H, Yukl SA, Ferre AL, Graf EH, Somsouk M, Sinclair E, Abdel-Mohsen M, Liegler T, Harvill K, Hoh R, et al.:
433 **Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers.** *PLoS Pathog* 2013,
434 **9**:e1003691.
- 435 31. Boufassa F, Lechenadec J, Meyer L, Costagliola D, Hunt PW, Pereyra F, Deeks S, Pancino G, Taulera O, Lichterfeld M,
436 et al.: **Blunted response to combination antiretroviral therapy in HIV elite controllers: an international HIV**
437 **controller collaboration.** *PLoS One* 2014, **9**:e85516.
- 438 32. Fukazawa Y, Lum R, Okoye AA, Park H, Matsuda K, Bae JY, Hagen SI, Shoemaker R, Deleage C, Lucero C, et al.: **B**
439 **cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite**
440 **controllers.** *Nat Med* 2015, **21**:132-139.
- 441 33. Dugast AS, Arnold K, Lofano G, Moore S, Hoffner M, Simek M, Pognard P, Seaman M, Suscovich TJ, Pereyra F, et al.:
442 **Virus-driven Inflammation Is Associated With the Development of bNAbs in Spontaneous Controllers of**
443 **HIV.** *Clin Infect Dis* 2017, **64**:1098-1104.
- 444 * This study identified a specific inflammation profile associated with the development of
445 neutralization breadth in EC.
- 446 34. Mabuka JM, Dugast AS, Muema DM, Reddy T, Ramlakhan Y, Euler Z, Ismail N, Moodley A, Dong KL, Morris L, et al.:
447 **Plasma CXCL13 but Not B Cell Frequencies in Acute HIV Infection Predicts Emergence of Cross-**
448 **Neutralizing Antibodies.** *Frontiers in Immunology* 2017, **8**.
- 449 35. Guan Y, Sajadi MM, Kamin-Lewis R, Fouts TR, Dimitrov A, Zhang Z, Redfield RR, DeVico AL, Gallo RC, Lewis GK:
450 **Discordant memory B cell and circulating anti-Env antibody responses in HIV-1 infection.** *Proc Natl Acad*
451 *Sci U S A* 2009, **106**:3952-3957.

- 452 36. Goujard C, Chaix ML, Lambotte O, Deveau C, Sinet M, Guergnon J, Courgnaud V, Rouzioux C, Delfraissy JF, Venet A,
453 et al.: **Spontaneous control of viral replication during primary HIV infection: when is "HIV controller"**
454 **status established?** *Clin Infect Dis* 2009, **49**:982-986.
- 455 37. Sáez-Cirión A, Lacabaratz C, Lambotte O, Versmisse P, Urrutia A, Boufassa F, Barré-Sinoussi F, Delfraissy J-F, Sinet
456 M, Pancino G, et al.: **HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and**
457 **peculiar cytotoxic T lymphocyte activation phenotype.** *Proceedings of the National Academy of Sciences of the*
458 *United States of America* 2007, **104**:6776-6781.
- 459 38. Richman DD, Wrin T, Little SJ, Petropoulos CJ: **Rapid evolution of the neutralizing antibody response to HIV type 1**
460 **infection.** *Proc Natl Acad Sci U S A* 2003, **100**:4144-4149.
- 461 39. Mahalanabis M, Jayaraman P, Miura T, Pereyra F, Chester EM, Richardson B, Walker B, Haigwood NL: **Continuous**
462 **viral escape and selection by autologous neutralizing antibodies in drug-naive human immunodeficiency**
463 **virus controllers.** *J Virol* 2009, **83**:662-672.
- 464 40. Freund NT, Wang H, Scharf L, Nogueira L, Horwitz JA, Bar-On Y, Golijanin J, Sievers SA, Sok D, Cai H, et al.:
465 **Coexistence of potent HIV-1 broadly neutralizing antibodies and antibody-sensitive viruses in a viremic**
466 **controller.** *Sci Transl Med* 2017, **9**.
- 467 ** This in-depth longitudinal characterization of the humoral response in a HLA-B*57+
468 viremic controller suggests that NAbs contribute to HIV control.
- 469 41. Havenar-Daughton C, Lee JH, Crotty S: **Tfh cells and HIV bnAbs, an immunodominance model of the HIV**
470 **neutralizing antibody generation problem.** *Immunol Rev* 2017, **275**:49-61.
- 471 42. Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, Foucat E, Dullaers M, Oh S, Sabzghabaei
472 N, et al.: **Human blood CXCR5(+)/CD4(+) T cells are counterparts of T follicular cells and contain specific**
473 **subsets that differentially support antibody secretion.** *Immunity* 2011, **34**:108-121.
- 474 43. Schultz BT, Teigler JE, Pissani F, Oster AF, Kraniias G, Alter G, Marovich M, Eller MA, Dittmer U, Robb ML, et al.:
475 **Circulating HIV-Specific Interleukin-21(+)/CD4(+) T Cells Represent Peripheral Tfh Cells with Antigen-**
476 **Dependent Helper Functions.** *Immunity* 2016, **44**:167-178.
- 477 44. Cohen K, Altfeld M, Alter G, Stamatatos L: **Early preservation of CXCR5+ PD-1+ helper T cells and B cell**
478 **activation predict the breadth of neutralizing antibody responses in chronic HIV-1 infection.** *J Virol* 2014,
479 **88**:13310-13321.
- 480 45. Locci M, Havenar-Daughton C, Landais E, Wu J, Kroenke MA, Arlehamn CL, Su LF, Cubas R, Davis MM, Sette A, et
481 al.: **Human circulating PD-1+CXCR3-CXCR5+ memory Tfh cells are highly functional and correlate with**
482 **broadly neutralizing HIV antibody responses.** *Immunity* 2013, **39**:758-769.
- 483 46. Roeder J, Maehara T, Ngoepe A, Ramsuran D, Muenchhoff M, Adland E, Aicher T, Kazer SW, Jooste P, Karim F, et al.:
484 **High-Frequency, Functional HIV-Specific T-Follicular Helper and Regulatory Cells Are Present Within**
485 **Germinal Centers in Children but Not Adults.** *Front Immunol* 2018, **9**:1975.
- 486 47. Chakrabarti LA, Simon V: **Immune mechanisms of HIV control.** *Curr Opin Immunol* 2010, **22**:488-496.
- 487 48. Soghoian DZ, Jessen H, Flanders M, Sierra-Davidson K, Cutler S, Pertel T, Ranasinghe S, Lindqvist M, Davis I, Lane K,
488 et al.: **HIV-specific cytolytic CD4 T cell responses during acute HIV infection predict disease outcome.** *Sci*
489 *Transl Med* 2012, **4**:123ra125.
- 490 49. Benati D, Galperin M, Lambotte O, Gras S, Lim A, Mukhopadhyay M, Nouel A, Campbell KA, Lemercier B, Claireaux
491 M, et al.: **Public T cell receptors confer high-avidity CD4 responses to HIV controllers.** *J Clin Invest* 2016,
492 **126**:2093-2108.
- 493 50. Galperin M, Farenc C, Mukhopadhyay M, Jayasinghe D, Decroos A, Benati D, Tan LL, Ciacchi L, Reid HH, Rossjohn J,
494 et al.: **CD4(+) T cell-mediated HLA class II cross-restriction in HIV controllers.** *Sci Immunol* 2018, **3**.

- 495 51. Claireaux M, Galperin M, Benati D, Nouel A, Mukhopadhyay M, Klingler J, de Truchis P, Zucman D, Hendou S,
496 Boufassa F, et al.: **A High Frequency of HIV-Specific Circulating Follicular Helper T Cells Is Associated with**
497 **Preserved Memory B Cell Responses in HIV Controllers.** *MBio* 2018, **9**.
- 498 ** This article reports a high frequency of HIV-specific circulating Tfh in EC, which
499 correlates with the induction of HIV-specific antibodies in functional assays.
- 500 52. Buranapraditkun S, Pissani F, Teigler JE, Schultz BT, Alter G, Marovich M, Robb ML, Eller MA, Martin J, Deeks S, et
501 al.: **Preservation of Peripheral T Follicular Helper Cell Function in HIV Controllers.** *J Virol* 2017, **91**.
- 502 53. Bruhns P, Jonsson F: **Mouse and human FcR effector functions.** *Immunol Rev* 2015, **268**:25-51.
- 503 54. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, Decker JM, Wycuff D, Harris L, Hawkins N, et
504 al.: **Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically**
505 **infected with human immunodeficiency virus type 1 subtypes B and C.** *J Virol* 2008, **82**:11651-11668.
- 506 55. Banerjee K, Klasse PJ, Sanders RW, Pereyra F, Michael E, Lu M, Walker BD, Moore JP: **IgG subclass profiles in**
507 **infected HIV type 1 controllers and chronic progressors and in uninfected recipients of Env vaccines.** *AIDS*
508 *research and human retroviruses* 2010, **26**:445-458.
- 509 56. Ackerman ME, Mikhailova A, Brown EP, Dowell KG, Walker BD, Bailey-Kellogg C, Suscovich TJ, Alter G:
510 **Polyfunctional HIV-Specific Antibody Responses Are Associated with Spontaneous HIV Control.** *PLOS*
511 *Pathogens* 2016, **12**:e1005315.
- 512 57. French Ma, Center RJ, Wilson KM, Fleyfel I, Fernandez S, Schorcht A, Stratov I, Kramski M, Kent SJ, Kelleher AD:
513 **Isotype-switched immunoglobulin G antibodies to HIV Gag proteins may provide alternative or additional**
514 **immune responses to 'protective' human leukocyte antigen-B alleles in HIV controllers.** *AIDS (London,*
515 *England)* 2013, **27**:519-528.
- 516 58. Sadanand S, Das J, Chung AW, Schoen MK, Lane S, Suscovich TJ, Streeck H, Smith DM, Little SJ, Lauffenburger DA,
517 et al.: **Temporal variation in HIV-specific IgG subclass antibodies during acute infection differentiates**
518 **spontaneous controllers from chronic progressors.** *Aids* 2018, **32**:443-450.
- 519 * This study highlights that temporal variations of Env-specific IgG subclasses during acute
520 HIV infection are predictive of HIV control. In particular, Env-specific IgG3 responses persist
521 longer in EC.
- 522 59. Tay MZ, Liu P, Williams LD, McRaven MD, Sawant S, Gurley TC, Xu TT, Dennison SM, Liao HX, Chenine AL, et al.:
523 **Antibody-Mediated Internalization of Infectious HIV-1 Virions Differs among Antibody Isotypes and**
524 **Subclasses.** *PLoS Pathog* 2016, **12**:e1005817.
- 525 60. Dugast AS, Stamatatos L, Tonelli A, Suscovich TJ, Licht AF, Mikell I, Ackerman ME, Streeck H, Klasse PJ, Moore JP,
526 et al.: **Independent evolution of Fc- and Fab-mediated HIV-1-specific antiviral antibody activity following**
527 **acute infection.** *Eur J Immunol* 2014, **44**:2925-2937.
- 528 61. Nabi R, Moldoveanu Z, Wei Q, Golub ET, Durkin HG, Greenblatt RM, Herold BC, Nowicki MJ, Kassaye S, Cho MW,
529 et al.: **Differences in serum IgA responses to HIV-1 gp41 in elite controllers compared to viral suppressors on**
530 **highly active antiretroviral therapy.** *PLoS One* 2017, **12**:e0180245.
- 531 * This study suggests that HIV-specific IgA responses are more prevalent and affinity
532 maturation of anti-gp41 IgA antibodies occurs to a greater extent in EC than in patients on
533 cART.
- 534 62. Wills S, Hwang KK, Liu P, Dennison SM, Tay MZ, Shen X, Pollara J, Lucas JT, Parks R, Rerks-Ngarm S, et al.: **HIV-1-**
535 **Specific IgA Monoclonal Antibodies from an HIV-1 Vaccinee Mediate Galactosylceramide Blocking and**
536 **Phagocytosis.** *J Virol* 2018, **92**.

- 537 63. Duchemin M, Khamassi M, Xu L, Tudor D, Bomsel M: **IgA Targeting Human Immunodeficiency Virus-1 Envelope**
538 **gp41 Triggers Antibody-Dependent Cellular Cytotoxicity Cross-Clade and Cooperates with gp41-Specific**
539 **IgG to Increase Cell Lysis.** *Front Immunol* 2018, **9**:244.
- 540 64. Martinez V, Costagliola D, Bonduelle O, N'Go N, Schnuriger A, Théodorou I, Clauvel JP, Sicard D, Agut H, Debré P, et
541 al.: **Combinaison of HIV-1- specific CD4 Th1 cell reponses and IgG2 antibodies is the best predictor for**
542 **persistence of long-term non progression.** *J Infect Dis; Journal of infectious disease* 2005, **191**:191:2053-2063.
- 543 65. Ngo-Giang-Huong N, Candotti D, Goubar a, Autran B, Maynard M, Sicard D, Clauvel JP, Agut H, Costagliola D,
544 Rouzioux C: **HIV type 1-specific IgG2 antibodies: markers of helper T cell type 1 response and prognostic**
545 **marker of long-term nonprogression.** *AIDS research and human retroviruses* 2001, **17**:1435-1446.
- 546 66. Alter G, Dowell KG, Brown EP, Suscovich TJ, Mikhailova A, Mahan AE, Walker BD, Nimmerjahn F, Bailey-Kellogg
547 C, Ackerman ME: **High-resolution definition of humoral immune response correlates of effective immunity**
548 **against HIV.** *Mol Syst Biol* 2018, **14**:e7881.
- 549 ** This system serology study revealed the multifaceted contributions of polyclonal
550 antibodies responses in EC. It suggests that biophysical features such as the IgG glycosylation
551 patterns may be predictive of viral control.
- 552 67. Tjiam MC, Sariputra L, Armitage JD, Taylor JP, Kelleher AD, Tan DB, Lee S, Fernandez S, French MA: **Control of**
553 **early HIV-1 infection associates with plasmacytoid dendritic cell-reactive opsonophagocytic IgG antibodies**
554 **to HIV-1 p24.** *AIDS* 2016, **30**:2757-2765.
- 555 68. Tjiam MC, Morshidi MA, Sariputra L, Martin JN, Deeks SG, Tan DBA, Lee S, Fernandez S, French MA: **Association of**
556 **HIV-1 Gag-Specific IgG Antibodies With Natural Control of HIV-1 Infection in Individuals Not Carrying**
557 **HLA-B*57: 01 Is Only Observed in Viremic Controllers.** *J Acquir Immune Defic Syndr* 2017, **76**:e90-e92.
- 558 69. Ranasinghe S, Flanders M, Cutler S, Soghoian DZ, Ghebremichael M, Davis I, Lindqvist M, Pereyra F, Walker BD,
559 Heckerman D, et al.: **HIV-specific CD4 T cell responses to different viral proteins have discordant**
560 **associations with viral load and clinical outcome.** *J Virol* 2012, **86**:277-283.
- 561 70. Chung AW, Navis M, Isitman G, Centre R, Finlayson R, Bloch M, Gelgor L, Kelleher A, Kent SJ, Stratov I: **Activation**
562 **of NK cells by ADCC responses during early HIV infection.** *Viral Immunol* 2011, **24**:171-175.
- 563 71. Chung AW, Isitman G, Navis M, Kramski M, Center RJ, Kent SJ, Stratov I: **Immune escape from HIV-specific**
564 **antibody-dependent cellular cytotoxicity (ADCC) pressure.** *Proc Natl Acad Sci U S A* 2011, **108**:7505-7510.
- 565 72. Chen X, Lin M, Qian S, Zhang Z, Fu Y, Xu J, Han X, Ding H, Dong T, Shang H, et al.: **The Early Antibody-Dependent**
566 **Cell-Mediated Cytotoxicity Response Is Associated With Lower Viral Set Point in Individuals With Primary**
567 **HIV Infection.** *Front Immunol* 2018, **9**:2322.
- 568 73. Forthal DN, Finzi A: **Antibody-dependent cellular cytotoxicity in HIV infection.** *AIDS* 2018, **32**:2439-2451.
- 569 74. Johansson SE, Rollman E, Chung AW, Center RJ, Hejdeman B, Stratov I, Hinkula J, Wahren B, Karre K, Kent SJ, et al.:
570 **NK cell function and antibodies mediating ADCC in HIV-1-infected viremic and controller patients.** *Viral*
571 *Immunol* 2011, **24**:359-368.
- 572 75. Smalls-Mantey A, Doria-Rose N, Klein R, Patamawenu A, Migueles SA, Ko SY, Hallahan CW, Wong H, Liu B, You L,
573 et al.: **Antibody-dependent cellular cytotoxicity against primary HIV-infected CD4+ T cells is directly**
574 **associated with the magnitude of surface IgG binding.** *J Virol* 2012, **86**:8672-8680.
- 575 76. Madhavi V, Wines BD, Amin J, Emery S, Group ES, Lopez E, Kelleher A, Sydney LSG, Center RJ, Hogarth PM, et al.:
576 **HIV-1 Env- and Vpu-Specific Antibody-Dependent Cellular Cytotoxicity Responses Associated with Elite**
577 **Control of HIV.** *J Virol* 2017, **91**.
- 578 77. Lambotte O, Pollara J, Boufassa F, Moog C, Venet A, Haynes BF, Delfraissy JF, Saez-Cirion A, Ferrari G: **High**
579 **antibody-dependent cellular cytotoxicity responses are correlated with strong CD8 T cell viral suppressive**
580 **activity but not with B57 status in HIV-1 elite controllers.** *PLoS One* 2013, **8**:e74855.

- 581 78. Bruel T, Guivel-Benhassine F, Lorin V, Lortat-Jacob H, Baleux F, Bourdic K, Noel N, Lambotte O, Mouquet H,
582 Schwartz O: **Lack of ADCC Breadth of Human Nonneutralizing Anti-HIV-1 Antibodies.** *J Virol* 2017, **91**.
- 583 79. Tomaras GD, Ferrari G, Shen X, Alam SM, Liao HX, Pollara J, Bonsignori M, Moody MA, Fong Y, Chen X, et al.:
584 **Vaccine-induced plasma IgA specific for the C1 region of the HIV-1 envelope blocks binding and effector**
585 **function of IgG.** *Proc Natl Acad Sci U S A* 2013, **110**:9019-9024.
- 586 80. Gillis C, Gouel-Cheron A, Jonsson F, Bruhns P: **Contribution of Human FcγR3 to Disease with Evidence from**
587 **Human Polymorphisms and Transgenic Animal Studies.** *Front Immunol* 2014, **5**:254.
- 588 81. Martin MP, Naranbhai V, Shea PR, Qi Y, Ramsuran V, Vince N, Gao X, Thomas R, Brumme ZL, Carlson JM, et al.:
589 **Killer cell immunoglobulin-like receptor 3DL1 variation modifies HLA-B*57 protection against HIV-1.** *J*
590 *Clin Invest* 2018, **128**:1903-1912.
- 591 82. Isitman G, Lisovsky I, Tremblay-McLean A, Kovacs C, Harris M, Routy JP, Bruneau J, Wainberg MA, Tremblay C,
592 Bernard NF: **Antibody-Dependent Cellular Cytotoxicity Activity of Effector Cells from HIV-Infected Elite**
593 **and Viral Controllers.** *AIDS Res Hum Retroviruses* 2016, **32**:1079-1088.
- 594 83. Alter G, Ottenhoff THM, Joosten SA: **Antibody glycosylation in inflammation, disease and vaccination.** *Semin*
595 *Immunol* 2018, **39**:102-110.
- 596 84. Lofano G, Gorman MJ, Yousif AS, Yu WH, Fox JM, Dugast AS, Ackerman ME, Suscovich TJ, Weiner J, Barouch D, et
597 al.: **Antigen-specific antibody Fc glycosylation enhances humoral immunity via the recruitment of**
598 **complement.** *Sci Immunol* 2018, **3**.
- 599 85. Ackerman ME, Crispin M, Yu X, Baruah K, Boesch AW, Harvey DJ, Dugast AS, Heizen EL, Ercan A, Choi I, et al.:
600 **Natural variation in Fc glycosylation of HIV-specific antibodies impacts antiviral activity.** *J Clin Invest* 2013,
601 **123**:2183-2192.
- 602 86. Barouch DH, Whitney JB, Moldt B, Klein F, Oliveira TY, Liu J, Stephenson KE, Chang HW, Shekhar K, Gupta S, et al.:
603 **Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus**
604 **monkeys.** *Nature* 2013, **503**:224-228.
- 605 87. Schoofs T, Klein F, Braunschweig M, Kreider EF, Feldmann A, Nogueira L, Oliveira T, Lorenzi JC, Parrish EH, Learn
606 GH, et al.: **HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1.**
607 *Science* 2016, **352**:997-1001.
- 608 88. Nishimura Y, Gautam R, Chun TW, Sadjadpour R, Foulds KE, Shingai M, Klein F, Gazumyan A, Golijanin J, Donaldson
609 M, et al.: **Early antibody therapy can induce long-lasting immunity to SHIV.** *Nature* 2017, **543**:559-563.
- 610 **** This study shows that passive immunotherapy during acute SHIV infection facilitates the**
611 **emergence of potent cytotoxic CD8+ T cell responses that contribute to a durable suppression**
612 **of virus replication.**
- 613 89. Su B, Xu K, Lederle A, Peressin M, Biedma ME, Laumond G, Schmidt S, Decoville T, Proust A, Lambotin M, et al.:
614 **Neutralizing antibodies inhibit HIV-1 transfer from primary dendritic cells to autologous CD4 T**
615 **lymphocytes.** *Blood* 2012, **120**:3708-3717.
- 616 90. Posch W, Steger M, Knackmuss U, Blatzer M, Baldauf HM, Doppler W, White TE, Hortnagl P, Diaz-Griffero F, Lass-
617 Florl C, et al.: **Complement-Opsonized HIV-1 Overcomes Restriction in Dendritic Cells.** *PLoS Pathog* 2015,
618 **11**:e1005005.
- 619 91. Veenhuis RT, Freeman ZT, Korleski J, Cohen LK, Massaccesi G, Tomasi A, Boesch AW, Ackerman ME, Margolick JB,
620 Blankson JN, et al.: **HIV-antibody complexes enhance production of type I interferon by plasmacytoid**
621 **dendritic cells.** *J Clin Invest* 2017, **127**:4352-4364.
- 622 92. Hamimi C, David A, Versmisse P, Weiss L, Bruel T, Zucman D, Appay V, Moris A, Ungeheuer MN, Lascoux-Combe C,
623 et al.: **Dendritic Cells from HIV Controllers Have Low Susceptibility to HIV-1 Infection In Vitro but High**
624 **Capacity to Capture HIV-1 Particles.** *PLoS One* 2016, **11**:e0160251.