

[Skip to Main Content](#)

ADVERTISEMENT

THE LANCET

Infectious Diseases

Search for...

Go search

All Content

This Journal Full Site

[Advanced Search](#)

- [Log in](#)
- [Register](#)
- [Log in](#)
- [Subscribe](#)
- [Claim](#)

Personal View | [Volume 3, ISSUE 11](#), P722-727, November 01, 2003

- [PDF \[289 KB\]](#)[Download PDF \[289 KB\]](#)
- [Figures](#)
 - [Figure Viewer](#)
 - [Download Figures \(PPT\)](#)
- [Save](#)
 - [Add To Online Library](#) Powered By Mendeley
 - [Add To My Reading List](#)
 - [Export Citation](#)
 - [Create Citation Alert](#)
- [Share](#)

Share on

 - [Facebook](#)
 - [Twitter](#)
 - [LinkedIn](#)
 - [Mendeley](#)
 - [Email](#)
 - [Sina Weibo](#)
- [more](#)
 - [Reprints](#)
 - [Request](#)
- [Top](#)

Effects of chloroquine on viral infections: an old drug against today's diseases

- [Dr Adrea Savarino](#)

Adrea Savarino

Correspondence

Correspondence: Dr Andrea Savarino, Laboratory of Viral Immunology, Department of Infectious Diseases, Università Cattolica del Sacro Cuore, Largo Agostino Gemelli 8, I-00168 Rome, Italy. Tel +39 06 30155374; fax +39 06 3054519

[Contact](#)

Affiliations

AS and RC are at the Department of Infectious Diseases, Università Cattolica del Sacro Cuore, Rome, Italy

[Search for articles by this author](#)

- [John R Boelaert](#)

John R Boelaert

Affiliations

JRB is at the Unit of Infectious Diseases, AZ Sint-Jan, Brugge, Belgium

[Search for articles by this author](#)

- [Antonio Cassone](#)

Antonio Cassone

Affiliations

AC and GM are at the Departments of Infectious Diseases and Parasitology, respectively, Istituto Superiore di Sanità, Rome

[Search for articles by this author](#)

- [Giancarlo Majori](#)

Giancarlo Majori

Affiliations

AC and GM are at the Departments of Infectious Diseases and Parasitology, respectively, Istituto Superiore di Sanità, Rome

[Search for articles by this author](#)

- [Roberto Cauda](#)

Roberto Cauda

Affiliations

AS and RC are at the Department of Infectious Diseases, Università Cattolica del Sacro Cuore, Rome, Italy

[Search for articles by this author](#)

Published: November, 2003 DOI: [https://doi.org/10.1016/S1473-3099\(03\)00806-5](https://doi.org/10.1016/S1473-3099(03)00806-5)



PlumX Metrics

[Previous Article Pott's puffy tumour: a rare clinical entity](#)

[Next Article The possibility of eliminating blinding trachoma](#)



Recommend this journal

to your librarian

ADVERTISEMENT

Summary

Chloroquine is a 9-aminoquinoline known since 1934. Apart from its well-known antimalarial effects, the drug has interesting biochemical properties that might be applied against some viral infections.

Chloroquine exerts direct antiviral effects, inhibiting pH-dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Its best-studied effects are those against HIV replication, which are being tested in clinical trials. Moreover, chloroquine has

immunomodulatory effects, suppressing the production/release of tumour necrosis factor α and interleukin 6, which mediate the inflammatory complications of several viral diseases. We review the available information on the effects of chloroquine on viral infections, raising the question of whether this old drug may experience a revival in the clinical management of viral diseases such as AIDS and severe acute respiratory syndrome, which afflict mankind in the era of globalisation.

- [View related content for this article](#)

Chloroquine is a 9-aminoquinoline that has been known since 1934. Specifically synthesised to be used as an antimalarial agent, chloroquine was subsequently shown to have immunomodulatory properties that have encouraged its application in the treatment of autoimmune diseases such as rheumatoid arthritis. For this specific pathology, chloroquine and its hydroxy-analogue hydroxychloroquine have represented a valid contribution to the available pharmacological tools, since they proved able to slow down the progress of the disease while showing limited toxicity.

[1](#)

Canadian rheumatology association

Canadian Consensus Conference on hydroxychloroquine.

J Rheumatol. 2000; 27: 2919-2921

- [PubMed](#)
- [Google Scholar](#)

Unfortunately, chloroquine is being gradually dismissed from antimalarial therapy and prophylaxis, due to the continuous emergence of chloroquine-resistant *Plasmodium falciparum* strains. However, the tolerability, low cost, and immunomodulatory properties of chloroquine/hydroxychloroquine are associated with biochemical effects that suggest a potential use in viral infections, some of whose symptoms may result from the inflammatory response.

[2](#)

- Savarino A
- Gennero L
- Sperber K
- Boelaert JR

The anti-HIV-1 activity of chloroquine.

J Clin Virol. 2001; 20: 131-135

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

,
[3](#)

- Boelaert JR
- Piette J
- Sperber K

The potential place of chloroquine in the treatment of HIV-1–infected patients.

J Clin Virol. 2001; 20: 137-140

- [Summary](#)
- [Full Text](#)

- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(43\)](#)
- [Google Scholar](#)

We raise the question of whether this old drug whose parent compound, quinine, was isolated in the late 19th century from the bark of the tropical cinchona tree, may experience a revival in the clinical management of viral diseases of the era of globalisation.

General biochemical and cellular effects of chloroquine

Both chloroquine and hydroxychloroquine are weak bases that are known to affect acid vesicles leading to dysfunction of several enzymes. Extracellularly, chloroquine/hydroxychloroquine is present mostly in a protonated form that, due to its positive charge, is incapable of crossing the plasma membrane. However, the non-protonated portion can enter the intracellular compartment, where, in turn, it becomes protonated in a manner inversely proportional to the pH, according to the Henderson-Hasselbach law. It is thus not surprising that chloroquine/hydroxychloroquine is concentrated within acidic organelles such as the endosome, Golgi vesicles, and the lysosomes, where the pH is low and most chloroquine/hydroxychloroquine molecules are positively charged.

[4](#)

- Ohkuma S
- Poole B

Cytoplasmic vacuolation of mouse peritoneal macrophages and the uptake into lysosomes of weakly basic substances.

J Cell Biol. 1981; 90: 656-664

- [Crossref](#)
- [PubMed](#)
- [Scopus \(308\)](#)
- [Google Scholar](#)

Chloroquine/hydroxychloroquine is extruded to the extracellular medium mostly by exocytosis and/or through the action of the multidrug resistance protein MRP-1, a cell surface drug transporter belonging to the ATP-binding cassette family, which also includes the more thoroughly studied P-glycoprotein.

[5](#)

- Pescarmona GP
- Morra E
- Aldieri E
- Ghigo D
- Bosia A

Movements of vesicles in eukaryotic cells: role of intravesicle protons as a fuel and modulation of their concentration by drugs or metabolic changes.

MRS Bull. 1998; 489: 212-217

- [Google Scholar](#)

[6](#)

- Vezmar M
- Georges E

Reversal of MRP-mediated doxorubicin resistance with quinoline-based drugs.

Biochem Pharmacol. 2000; 59: 1245-1252

- [Crossref](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

,

7

- Vezmar M
- Georges E

Direct binding of chloroquine to the multidrug resistance protein (MRP): possible role for MRP in chloroquine drug transport and resistance in tumor cells.

Biochem Pharmacol. 1998; 56: 733-742

- [Crossref](#)
- [PubMed](#)
- [Scopus \(54\)](#)
- [Google Scholar](#)

It is well established that weak bases, by increasing the pH of lysosomal and trans-Golgi network (TGN) vesicles, disrupt several enzymes including acid hydrolases and inhibit the post-translational modification of newly synthesized proteins. The chloroquine-mediated rise in endosomal pH modulates iron metabolism within human cells by impairing the endosomal release of iron from ferrated transferrin, thus decreasing the intracellular concentration of iron. This decrease in turn affects the function of several cellular enzymes involved in pathways leading to replication of cellular DNA and to expression of different genes.

8

- Byrd TF
- Horwitz MA

Chloroquine inhibits the intracellular multiplication of *Legionella pneumophila* by limiting the availability of iron. A potential new mechanism for the therapeutic effect of chloroquine against intracellular pathogens.

J Clin Invest. 1991; 88: 351-357

- [Crossref](#)
- [PubMed](#)
- [Scopus \(100\)](#)
- [Google Scholar](#)

,

9

- Legssyer R
- Josse C
- Piette J
- Ward RJ
- Crichton RR

Changes in function of iron-loaded alveolar macrophages after in vivo administration of desferrioxamine and/or chloroquine.

J Inorg Biochem. 2003; 94: 36-42

- [Crossref](#)
- [PubMed](#)
- [Scopus \(20\)](#)
- [Google Scholar](#)

General mechanisms of viral inhibition by chloroquine

Chloroquine/hydroxychloroquine can impair the replication of several viruses by interacting with the endosome-mediated viral entry or the late stages of replication of enveloped viruses ([figure 1](#)).

Figure thumbnail gr1

Figure 1 Steps of the replication of different viruses affected by chloroquine (marked by red rectangles). Chloroquine inhibits the replication of different viruses either at the early or late stages of viral replication.

- [View Large Image](#)
- [Figure Viewer](#)
- [Download Hi-res image](#)
- [Download \(PPT\)](#)

Endosome-mediated viral entry interaction

Some viruses enter their target cells by endocytosis. This process targets the virus to the lysosomal compartment where the low pH, along with the action of enzymes, disrupts the viral particle, thus liberating the infectious nucleic acid and, in several cases, enzymes necessary for viral replication. Chloroquine has been shown to inhibit different viruses requiring a pH-dependent step for entry, such as the Borna disease virus, [10](#)

- Gonzalez-Dunia D
- Cubitt B
- de la Torre JC

Mechanism of Borna disease virus entry into cells.

J Virol. 1998; 72: 783-788

- [PubMed](#)
- [Google Scholar](#)

the minute virus of mice MVMp,

[11](#)

- Ros C
- Burckhardt CJ
- Kempf C

Cytoplasmic trafficking of minute virus of mice: low-pH requirement, routing to late endosomes, and proteasome interaction.

J Virol. 2002; 76: 12634-12645

- [Crossref](#)
- [PubMed](#)
- [Scopus \(62\)](#)

- [Google Scholar](#)

and the avian leucosis virus.

[12](#)

- Diaz-Griffero F
- Hoschander SA
- Brojatsch J

Endocytosis is a critical step in entry of subgroup B avian leukosis viruses.

J Virol. 2000; 76: 12866-12876

- [Crossref](#)
- [Scopus \(59\)](#)
- [Google Scholar](#)

Of particular interest for human pathology is the report that chloroquine inhibits uncoating of the hepatitis A virus, thus blocking its entire replication cycle.

[13](#)

- Bishop NE

Examination of potential inhibitors of hepatitis A virus uncoating.

Intervirology. 1998; 41: 261-271

- [Crossref](#)
- [PubMed](#)
- [Scopus \(35\)](#)
- [Google Scholar](#)

Replication of enveloped viruses interaction

For some enveloped viruses, post-translational modification of the envelope glycoproteins occurs within the endoplasmic and TGN vesicles. This process involves proteases and glycosyl-transferases, some of which require a low pH. In line with the pH-dependence of these events, chloroquine was seen to inhibit budding of Mayaro virus particles,

[14](#)

- Ferreira DF
- Santo MP
- Rebello MA
- Rebello MC

Weak bases affect late stages of Mayaro virus replication cycle in vertebrate cells.

J Med Microbiol. 2000; 49: 313-318

- [PubMed](#)
- [Google Scholar](#)

and to induce accumulation of non-infectious herpes simplex virus 1 particles in the TGN.

[15](#)

- Harley CA
- Dasgupta A
- Wilson DW

Characterization of herpes simplex virus-containing organelles by subcellular fractionation: role for organelle acidification in assembly of infectious particles.

J Virol. 2001; 75: 1236-1251

- [Crossref](#)
- [PubMed](#)
- [Scopus \(107\)](#)
- [Google Scholar](#)

Chloroquine also inhibits the replication of members of the Flaviviridae family by affecting the normal proteolytic processing of the flavivirus prM protein to M.

[16](#)

- Randolph VB
- Winkler G
- Stollar V

Acidotropic amines inhibit proteolytic processing of flavivirus prM protein.

Virology. 1990; 174: 450-458

- [Crossref](#)
- [PubMed](#)
- [Scopus \(125\)](#)
- [Google Scholar](#)

As a result, viral infectivity is impaired. Finally, chloroquine induces the production of non-infectious retrovirus particles, as shown with the avian reticuloendotheliosis virus REV-A and with HIV-1.

[17](#)

- Tsai WP
- Nara PL
- Kung HF
- Oroszlan S

Inhibition of human immunodeficiency virus infectivity by chloroquine.

AIDS Res Hum Retroviruses. 1990; 6: 481-489

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

The mechanism of inhibition seems to be inhibition of glycosylation of the envelope glycoproteins, as will be discussed below.

Effects of chloroquine on the immune system

The accumulation of chloroquine/hydroxychloroquine in lymphocytes and macrophages results in anti-inflammatory properties, and has led to its clinical use in conditions such as rheumatoid arthritis, lupus erythematosus, and sarcoidosis, the last being characterised by an overproduction of tumour necrosis factor α (TNF α) by the alveolar macrophages.

[18](#)

- Baughman RP
- Lower EE

- du Bois RM

Sarcoidosis.

Lancet. 2003; 361: 1111-1118

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(558\)](#)
- [Google Scholar](#)

Chloroquine/hydroxychloroquine reduces the secretion of these proinflammatory cytokines and in particular TNF α , as shown in a murine macrophage cell line,

[19](#)

- Jeong J-Y
- Jue D-M

Chloroquine inhibits processing of tumor necrosis factor in lipopolysaccharidestimulated RAW 264·7 macrophages.

J Immunol. 1997; 158: 4901-4907

- [PubMed](#)
- [Google Scholar](#)

and in primary cells such as mouse peritoneal macrophages,

[20](#)

- Bondeson J
- Sundler R

Antimalarial drugs inhibit phospholipase A2 activation and induction of interleukin β and tumor necrosis factor α in macrophages.

General Pharmacol. 1998; 30: 357-366

- [Crossref](#)
- [PubMed](#)
- [Scopus \(48\)](#)
- [Google Scholar](#)

human peripheral blood mononuclear cells,

[21](#)

- Van den Borne BE
- Dijkmans BA
- de Rooij HH
- le Cessie S
- Verweij CL

Chloroquine and hydroxychloroquine equally affect tumor necrosis factor- α , interleukin 6 and interferon- γ production by peripheral blood mononuclear cells.

J Rheumatol. 1997; 24: 55-60

- [PubMed](#)
- [Google Scholar](#)

and human whole blood.

[22](#)

- Karres I
- Kremer J-P
- Dietl I
- Steckholzer U
- Jochum M
- Ertel W

Chloroquine inhibits proinflammatory cytokine release into human whole blood.

Am J Physiol. 1998; 274: R1058-R1064

- [PubMed](#)
- [Google Scholar](#)

Several mechanisms have been evoked to explain the chloroquine/hydroxychloroquine-induced inhibition of TNF α production by monocyte-macrophages: disruption of cellular iron homeostasis,

[23](#)

- Picot S
- Peyron F
- Donadille A
- Vuillez J-P
- Barbe G
- Ambroise-Thomas P

Chloroquine-induced inhibition of the production of TNF, but not of IL-6, is affected by disruption of iron metabolism.

Immunology. 1993; 80: 127-133

- [PubMed](#)
- [Google Scholar](#)

inhibition of TNF α mRNA expression,

[20](#)

- Bondeson J
- Sundler R

Antimalarial drugs inhibit phospholipase A2 activation and induction of interleukin β and tumor necrosis factor α in macrophages.

General Pharmacol. 1998; 30: 357-366

- [Crossref](#)
- [PubMed](#)
- [Scopus \(48\)](#)
- [Google Scholar](#)

inhibition at a pretranslational stage by a non-lysosomotropic mechanism,

[24](#)

- Weber SM
- Levitz SM

Chloroquine interferes with lipopolysaccharide-induced TNF- α gene expression by a nonlysosomotropic

mechanism.

J Immunol. 2000; 165: 1534-1540

- [Crossref](#)
- [PubMed](#)
- [Scopus \(109\)](#)
- [Google Scholar](#)

or at a post-translational stage by blocking the conversion from cell-associated pro-TNF α to a soluble mature form.

[19](#)

- Jeong J-Y
- Jue D-M

Chloroquine inhibits processing of tumor necrosis factor in lipopolysaccharidestimulated RAW 264·7 macrophages.

J Immunol. 1997; 158: 4901-4907

- [PubMed](#)
- [Google Scholar](#)

Apart from inhibiting TNF α production by stimulated monocyte-macrophages, chloroquine also decreases the surface expression of TNF α receptors in human monocytic cell lines and, hence, the receptor-mediated TNF α signalling.

[25](#)

- Jeong J-Y
- Choi JW
- Jeon K-I
- Jue D-M

Chloroquine decreases cell-surface expression of tumour necrosis factor receptors in human histiocytic U-937 cells.

Immunol. 2002; 105: 83-91

- [Crossref](#)
- [PubMed](#)
- [Scopus \(26\)](#)
- [Google Scholar](#)

The results of such an impairment of TNF α -mediated signalling are shown in [figure 2](#).

Figure thumbnail gr2

Figure 2 Effects of chloroquine on the immune system. TNF α is produced by activated monocytes/macrophages. Among its multiple functions it helps to activate resting monocytes and favours extravasation of neutrophils by opening tight junctions between human vascular endothelial cells and upregulating leucocyte adhesion molecules (LAM).

[26](#)

- Nooteboom A
- Hendriks T
- Otteholler I
- van der Linden CJ

Permeability characteristics of human endothelial monolayers seeded on different

extracellular matrix proteins.

Mediators Inflamm. 2000; 9: 235-241

- [Crossref](#)
- [PubMed](#)
- [Scopus \(33\)](#)
- [Google Scholar](#)

Chloroquine diminishes TNF α production and downregulates the TNF α receptors 1 and 2 (TNFR) on the monocyte cell surface, which eventually results in decreased monocyte activation as well as decreased leucocyte extravasation. Red crosses mark the steps directly inhibited by chloroquine.

- [View Large Image](#)
- [Figure Viewer](#)
- [Download Hi-res image](#)
- [Download \(PPT\)](#)

Safety considerations

The studies reviewed here show that chloroquine/ hydroxychloroquine has in-vitro antiviral effects and anti-inflammatory properties that may be of interest in those viral infections associated with inflammation and/or immune activation. Before analysing the potential effects of a drug on a disease, safety criteria have to be met, to estimate the risk/benefit ratio.

Chloroquine/hydroxychloroquine has a well-studied toxicity profile. The half-century-long use of this drug in the therapy of malaria demonstrates the safety of acute administration of chloroquine to human beings. The use of chloroquine/hydroxychloroquine in rheumatic diseases and for antimalarial prophylaxis showed a low incidence of adverse events during chronic administration of this drug for periods of up to a few years. In these cases, the most serious toxic effect is a macular retinopathy, which depends on the cumulative dose rather than on the daily dose, and permanent damage may be prevented with regular visual monitoring during treatment.

[27](#)

- Bernstein HN

Ocular safety of hydroxychloroquine.

Ann Ophthalmol. 1991; 23: 292-296

- [PubMed](#)
- [Google Scholar](#)

[28](#)

- Bernstein HN

Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy.

Am J Med. 1983; 75: 25-34

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(104\)](#)
- [Google Scholar](#)

29

- Herman K
- Leys A
- Spileers W

(Hydroxy)-chloroquine retinal toxicity: two case reports and safety guidelines.

Bull Soc Belge Ophtalmol. 2002; 284: 21-29

- [PubMed](#)
- [Google Scholar](#)

A recent study

30

- Klinger G
- Morad Y
- Westall CA
- et al.

Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases.

Lancet. 2001; 358: 813-814

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(94\)](#)
- [Google Scholar](#)

provided encouraging results on the safety of a high dosage of the drug (up to 500 mg of chloroquine base per day) even during pregnancy.

We conclude that chloroquine/hydroxychloroquine administration presents limited and well-preventable toxicity and may thus result in a low risk/benefit balance at least when it is used in life-threatening conditions.

Henceforth, we will discuss the potential usefulness of this old drug in the treatment of two infectious diseases posing a serious threat to public health in the era of globalisation, AIDS and severe acute respiratory syndrome (SARS). These diseases are both caused by enveloped RNA viruses, and share some clinical manifestations that are likely to be mediated by immune reactions of the host.

Effects on HIV infection

Anti-HIV effects of chloroquine

Under testing conditions intended to mimic as best as possible clinical situations, chloroquine/hydroxychloroquine is capable of inhibiting HIV in vitro. This ability was shown either by overloading the cells with high concentrations of chloroquine/hydroxychloroquine before the infection,

17

- Tsai WP
- Nara PL
- Kung HF
- Oroszlan S

Inhibition of human immunodeficiency virus infectivity by chloroquine.

AIDS Res Hum Retroviruses. 1990; 6: 481-489

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

,
[31](#)

- Sperber K
- Kalb TH
- Stecher VJ
- Banerjee R
- Mayer L

Inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes.

AIDS Res Hum Retroviruses. 1993; 9: 91-98

- [Crossref](#)
- [PubMed](#)
- [Scopus \(100\)](#)
- [Google Scholar](#)

so as to mimic the drug build-up taking place in the tissues of patients subject to chronic treatment, or by keeping HIV-infected cells under constant incubation with concentrations of chloroquine detected in whole blood of individuals chronically treated with this drug.

[32](#)

- Pardridge WM
- Yang J
- Diagne A

Chloroquine inhibits HIV-1 replication in human peripheral blood lymphocytes.

Immunol Lett. 1998; 64: 45-47

- [Crossref](#)
- [PubMed](#)
- [Scopus \(24\)](#)
- [Google Scholar](#)

,
[33](#)

- Savarino A
- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.

AIDS. 2001; 15: 2221-2229

- [Crossref](#)
- [PubMed](#)

- [Scopus \(93\)](#)
- [Google Scholar](#)

The anti-HIV activity of chloroquine has been shown not only in cell line models, but also in peripheral blood lymphocytes and monocytes

[31](#)

- Sperber K
- Kalb TH
- Stecher VJ
- Banerjee R
- Mayer L

Inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes.

AIDS Res Hum Retroviruses. 1993; 9: 91-98

- [Crossref](#)
- [PubMed](#)
- [Scopus \(100\)](#)
- [Google Scholar](#)

,
[33](#)

- Savarino A
- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.

AIDS. 2001; 15: 2221-2229

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

—ie, cell culture models in which cellular uptake of chloroquine is closer to the conditions occurring in vivo. Under these conditions, it was possible to obtain levels of inhibition of viral replication above 90%. That hydroxychloroquine has some antiviral activity in vivo has been reported by two phase II clinical trials.

[34](#)

- Sperber K
- Louie M
- Kraus T
- et al.

Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1.

Clin Ther. 1995; 17: 622-636

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(101\)](#)

- [Google Scholar](#)

35

- Sperber K
- Chiang G
- Chen H
- et al.

Comparison of hydroxychloroquine with zidovudine in asymptomatic patients infected with HIV-1.

Clin Ther. 1997; 19: 913-923

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

The first trial was a small randomised, doubleblind, placebo-controlled pilot study on 40 patients (20 patients per arm), 27 of them being antiretroviral treatment-naive. Hydroxychloroquine administration for 8 weeks resulted in a mean 0.6 log reduction in plasma HIV-1 RNA copy numbers ($p=0.02$) as well as in a decrease in interleukin 6 concentrations, whereas placebo did not have any effects on both HIV-1 RNA and interleukin 6.

34

- Sperber K
- Louie M
- Kraus T
- et al.

Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1.

Clin Ther. 1995; 17: 622-636

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(101\)](#)
- [Google Scholar](#)

The second trial was also a small randomised, double-blinded trial, comparing the effectiveness of hydroxychloroquine with that of zidovudine monotherapy for 16 weeks in 72 patients, 64 of whom being antiretroviral treatment-naive (35 in the hydroxychloroquine arm and 37 in the zidovudine arm). Hydroxychloroquine again significantly reduced the plasma HIV-1 RNA copy numbers/mL (baseline 39 456 [31 000]; post-treatment 16 434 [11 373]; mean log reduction 0.4; $p=0.02$), though less than zidovudine (baseline 42 709 [33 050]; post-treatment 11 228 [7459]; mean log reduction 0.6; $p=0.01$). Since eight of 37 people in the zidovudine group, but none of the 35 individuals in the hydroxychloroquine group, showed an increase in the HIV-1 RNA levels and in the cultured virus levels during therapy, these data are consistent with the hypothesis that resistance to hydroxychloroquine may not easily develop as opposed to the well-known development of resistance to monotherapy with other antiretrovirals such as zidovudine.

35

- Sperber K
- Chiang G

- Chen H
- et al.

Comparison of hydroxychloroquine with zidovudine in asymptomatic patients infected with HIV-1.
Clin Ther. 1997; 19: 913-923

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

The results of larger clinical trials will be necessary for an accurate analysis of any possible discrepancies between the effects of chloroquine in vitro and in HIV-infected individuals.

Some of us have recently shown that chloroquine, at nontoxic, clinically achievable concentrations, has in-vitro activity against primary isolates belonging to different HIV-1 and HIV-2 clades.

[33](#)

- Savarino A
- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.
AIDS. 2001; 15: 2221-2229

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

The mechanism of the anti-HIV effects of chloroquine/hydroxychloroquine is a reduction in the infectivity of newly produced virions (reviewed in Savarino et al

[2](#)

- Savarino A
- Gennero L
- Sperber K
- Boelaert JR

The anti-HIV-1 activity of chloroquine.
J Clin Virol. 2001; 20: 131-135

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

). The antiviral effects of chloroquine are associated with the reduced production of the heavily glycosylated epitope 2G12, which is located on the gp120 envelope glycoprotein surface and is fundamental for virus infectivity.

[33](#)

- Savarino A

- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.
AIDS. 2001; 15: 2221-2229

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

These effects are likely to be attributed to the increased pH in TGN, which impairs the function of glycosyl-transferases involved in the post-translational processing of the HIV glycoproteins.

[2](#)

- Savarino A
- Gennero L
- Sperber K
- Boelaert JR

The anti-HIV-1 activity of chloroquine.
J Clin Virol. 2001; 20: 131-135

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

,

[17](#)

- Tsai WP
- Nara PL
- Kung HF
- Oroszlan S

Inhibition of human immunodeficiency virus infectivity by chloroquine.
AIDS Res Hum Retroviruses. 1990; 6: 481-489

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

,

[33](#)

- Savarino A
- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.

AIDS. 2001; 15: 2221-2229

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

HIV glycosylation may therefore represent a new target for antiretroviral therapy. As viral envelope glycosylation is mediated by cellular enzymes, its inhibition may explain the broad spectrum of the in-vitro anti-HIV activity of chloroquine against all major subtypes of HIV-1 and HIV-2.

[33](#)

- Savarino A
- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.

AIDS. 2001; 15: 2221-2229

- [Crossref](#)
- [PubMed](#)
- [Scopus \(93\)](#)
- [Google Scholar](#)

The effect of chloroquine/hydroxychloroquine on cellular rather than viral enzymes may also result in a low propensity to resistance development.

Effects of chloroquine in combination with other antiretrovirals

As chloroquine/hydroxychloroquine probably inhibits viral replication by a mechanism different from those of currently used antiretroviral drugs, its application has been studied in combination with other antiretroviral drugs. The use of chloroquine in combination with other antiretrovirals is theoretically supported by the observation that chloroquine also shows anti-HIV activity in vitro towards isolates from patients in therapeutic failure with a multidrug-resistant profile.

[36](#)

Debiaggi M, Bruno R, Sacchi P, Filice G. Antiviral activity of chloroquine against HIV-1 strains resistant to antiretroviral drugs. *Antiviral Res* (in press)

- [Google Scholar](#)

First, hydroxychloroquine has an additive in vitro anti-HIV effect to that of zidovudine.

[37](#)

- Chiang G
- Sassaroli M
- Louie M
- Chen H
- Stecher VJ
- Sperber K

Inhibition of HIV-1 replication by hydroxychloroquine: mechanism of action and comparison with zidovudine.

Clin Ther. 1996; 18: 1080-1092

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(65\)](#)
- [Google Scholar](#)

Second, chloroquine exerts in vitro an additive anti-HIV-1 effect on the combinations of hydroxyurea plus didanosine or hydroxyurea plus zidovudine in T-cell lines, monocytes, and primary T-cells.

[2](#)

- Savarino A
- Gennero L
- Sperber K
- Boelaert JR

The anti-HIV-1 activity of chloroquine.

J Clin Virol. 2001; 20: 131-135

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(74\)](#)
- [Google Scholar](#)

,
[38](#)

- Boelaert JR and Sperber K

Antiretroviral therapy.

Lancet. 1998; 352: 1224-1225

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(11\)](#)
- [Google Scholar](#)

,
[39](#)

- Boelaert JR
- Sperber K
- Piette J

Chloroquine exerts an additive in vitro anti-HIV-1 effect, when combined to zidovudine and hydroxyurea.

Biochem Pharmacol. 2001; 61: 1531-1535

- [Crossref](#)
- [PubMed](#)
- [Scopus \(18\)](#)
- [Google Scholar](#)

The didanosine/hydroxyurea/hydroxychloroquine combination, especially attractive for developing

countries due to its low cost, was tested clinically in Singapore in an open study. Of the initial 22 patients who started the study, six were withdrawn due to non-compliance. In the remaining 16 patients, HIV-1 RNA plasma levels decreased by a mean of 1.3 log at week 12 and 48.

[40](#)

- Paton NI
- Aboulhab J
- Karim F

Hydroxychloroquine, hydroxycarbamide, and didanosine as economic treatment for HIV-1.
Lancet. 2002; 359: 1667-1668

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(40\)](#)
- [Google Scholar](#)

In a smaller study, with didanosine/hydroxyurea/chloroquine, HIV-1 RNA remained lowered by a mean of 2.5 log after more than 96 weeks.

[41](#)

- Boelaert JR
- Dom GM
- Huitema AD
- Beijnen JH
- Lange JM

The boosting of didanosine by allopurinol permits a halving of the didanosine dosage.
AIDS. 2002; 16: 2221-2223

- [Crossref](#)
- [PubMed](#)
- [Scopus \(10\)](#)
- [Google Scholar](#)

These open pilot studies do not yet allow a determination of the contribution of chloroquine/hydroxychloroquine to the viral load drop. However, it can be concluded that the addition of chloroquine/hydroxychloroquine to hydroxyurea and didanosine is potentially safe, thus encouraging the design of larger studies with multiple arms.

Prevention of HIV transmission via breastfeeding

It is possible to hypothesise that chloroquine may find a potential application in prevention of mother-to-child transmission (MTCT) of HIV through breastfeeding, a problem still far from being solved in resource-poor countries.

[42](#)

- Mofenson LM
- McIntyre JA

Advances and research directions in the prevention of mother-to-child HIV-1 transmission.
Lancet. 2000; 355: 2237-2244

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(168\)](#)
- [Google Scholar](#)

One of us reported a 243-fold accumulation of chloroquine in colostrum cells of Burkinabà mothers taking 100 mg of chloroquine daily and hypothesised that such a high degree of chloroquine accumulation in mammary cells actively replicating HIV-1 may allow a decrease in milk viral load and/or infectivity of milk and, hence, may lower the risk of breastfeeding-related transmission,

[43](#)

- Boelaert JR
- Yaro S
- Augustijns P
- et al.

Chloroquine accumulates in breast milk cells. Potential impact as adjuvant to antiretroviral prophylaxis for postnatal mother-to-child transmission of HIV-1.

AIDS. 2001; 15: 2205-2206

- [Crossref](#)
- [PubMed](#)
- [Scopus \(25\)](#)
- [Google Scholar](#)

which accounts for one-third to one-half of HIV-1 MTCTs.

[44](#)

- DeCock KM
- Fowler MG
- Mercier E
- et al.

Prevention of mother-to-child transmission of HIV-1 in resource-poor countries: translating research into policy and practice.

JAMA. 2000; 283: 1175-1182

- [Crossref](#)
- [PubMed](#)
- [Scopus \(731\)](#)
- [Google Scholar](#)

Therefore the CHARGE (Chloroquine Administration to Reduce HIV-1 Genome Exposure) study was set up, being a placebocontrolled pilot study in breastfeeding mothers (having received, together with their infant, peripartum nevirapine), that will assess whether daily chloroquine administration compared with placebo administration to the mother during the early months of breastfeeding may result in decreased HIV-1 RNA milk levels and/or decreased ex vivo infectivity of virions isolated from milk.

Decrease of excessive immune activation

The chloroquine/hydroxychloroquine-induced suppression of the synthesis of proinflammatory cytokines such as TNF α may be beneficial in decreasing the inappropriate immune activation characteristic of HIV infection. This may be particularly useful to people with HIV/AIDS in the developing world, who,

probably due to concomitant infections, present higher levels of TNF α production and of immune activation than those from the developed world.

[45](#)

- Corbett EL
- Steketee RW
- ter Kuile FO
- Latif AS
- Kamali A
- Hayes RJ

HIV-1/AIDS and the control of other infectious diseases in Africa.

Lancet. 2002; 359: 2177-2187

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(169\)](#)
- [Google Scholar](#)

,

[46](#)

- Clerici M
- Butto S
- Lukwiya M
- et al.

Immune activation in Africa is environmentally driven and is associated with upregulation of CCR5.

AIDS. 2000; 14: 2083-2092

- [Crossref](#)
- [PubMed](#)
- [Scopus \(107\)](#)
- [Google Scholar](#)

,

[47](#)

- Bentwich Z
- Maartens G
- Torten D
- Lal AA
- Lal RB

Concurrent infections and HIV pathogenesis.

AIDS. 2000; 14: 2071-2081

- [Crossref](#)
- [PubMed](#)
- [Scopus \(108\)](#)
- [Google Scholar](#)

Chloroquine/hydroxychloroquine should be studied, particularly in areas with high prevalence of HIV-1C,

such as southern Africa. Indeed, when TNF α is used for in-vitro stimulation, the rate of transcriptional activation of HIV-1 is higher for HIV-1C than for HIV-1B and HIV-1 CRF_1AE. Such an enhanced capacity to respond to TNF α may be related to the extra NF-kappaB binding site(s) present in the long terminal repeat of the HIV-1C genome.

[48](#)

- Montano MA
- Nixon CP
- Ndung'u T
- et al.

Elevated tumor necrosis factor- α activation of human immunodeficiency virus subtype 1 in southern Africa is associated with an NF-kB enhancer gain-of-function.

J Infect Dis. 2000; 181: 76-81

- [Crossref](#)
- [PubMed](#)
- [Scopus \(79\)](#)
- [Google Scholar](#)

Hypothesis: the case of SARS

Based on the effects of chloroquine/hydroxychloroquine on several enveloped viruses and on immune activation, we raise the hypothesis that this drug might be of some use for the clinical management of SARS. At present, any attempt to treat this disease with known antiviral drugs—namely ribavirin and oseltamivir—has been inconclusive.

[49](#)

- Poutanen SM
- Low DE
- Henry B
- et al.

Identification of severe acute respiratory syndrome in Canada.

N Engl J Med. 2003; 348: 1995-2005

- [Crossref](#)
- [PubMed](#)
- [Scopus \(902\)](#)
- [Google Scholar](#)

Corticosteroids may be of some benefit in controlling the inflammatory response at the lung level

[50](#)

- So LK
- Lau AC
- Yam LY
- et al.

Development of a standard treatment protocol for severe acute respiratory syndrome.

Lancet. 2003; 361: 1615-1617

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)

- [PubMed](#)
- [Scopus \(258\)](#)
- [Google Scholar](#)

but may also cause uncontrolled immunodepression resulting in pulmonary superinfection. The causative agent of SARS has recently been described as a new coronavirus.

[51](#)

- Peiris JS
- Lai ST
- Poon LL
- et al.

Coronavirus as a possible cause of severe acute respiratory syndrome.

Lancet. 2003; 361: 1319-1325

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(1871\)](#)
- [Google Scholar](#)

[52](#)

- Drosten C
- Gunther S
- Preiser W
- et al.

Identification of a novel coronavirus in patients with severe acute respiratory syndrome.

N Engl J Med. 2003; 348: 1967-1976

- [Crossref](#)
- [PubMed](#)
- [Scopus \(2417\)](#)
- [Google Scholar](#)

Recent studies support the idea that coronaviridae infect their target cells by an endocytic pathway and that chloroquine might inhibit their replication.

[53](#)

- Blau D
- Holmes K

Human Coronavirus HCoV-229E enters susceptible cells via the endocytic pathway.

in: Lavi E The Nidoviruses, Coronaviruses and Arteriviruses. Kluwer, New York2001: 193-197

- [Google Scholar](#)

[54](#)

- Nauwynck HJ
- Duan X

- Favoreel HW
- Van Oostveldt P
- Pensaert MB

Entry of porcine reproductive and respiratory syndrome virus into porcine alveolar macrophages via receptor-mediated endocytosis.

J Gen Virol. 1999; 80: 297-305

- [PubMed](#)
- [Google Scholar](#)

Cells infected with the human coronavirus HCoV-229E and treated with nocodazole (a microtubuledepolymerising agent that blocks transport from early to late endosomes) produced decreased amounts of HCoV-229E antigens.

[53](#)

- Blau D
- Holmes K

Human Coronavirus HCoV-229E enters susceptible cells via the endocytic pathway.

in: Lavi E *The Nidoviruses, Coronaviruses and Arteriviruses.* Kluwer, New York2001: 193-197

- [Google Scholar](#)

This result indicates that endosomal transport is needed for HCoV-229E infection. Cells treated with chloroquine expressed decreased amounts of HCoV-229E antigens.

[53](#)

- Blau D
- Holmes K

Human Coronavirus HCoV-229E enters susceptible cells via the endocytic pathway.

in: Lavi E *The Nidoviruses, Coronaviruses and Arteriviruses.* Kluwer, New York2001: 193-197

- [Google Scholar](#)

Preliminary data obtained from our group confirm these reports and show that chloroquine potently inhibits the replication of a canine coronavirus at therapeutically reachable concentrations (C Buonavoglia et al, University of Bari, Italy; unpublished). Although the SARS coronavirus is distinct with unique characteristics, it is tempting to ask whether chloroquine might affect SARS coronavirus replication as well.

The anti-inflammatory properties of chloroquine/hydroxychloroquine should also be considered. The clinical worsening of individuals with SARS in week 2 is apparently unrelated to uncontrolled SARS coronavirus replication but may be related to immunopathological damage.

[55](#)

- Peiris JS
- Chu CM
- Cheng VC
- et al.

Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.

Lancet. 2003; 361: 1767-1772

- [Summary](#)

- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(1318\)](#)
- [Google Scholar](#)

A model taking into account the role of proinflammatory cytokines could help interpret this event ([figure 3](#)). This view is derived from the effects of the porcine respiratory coronavirus (PRCV), which shares with the SARS coronavirus the ability to cause a disease with similar histopathological features and symptomatology.

[57](#)

- Nicholls JM
- Poon LL
- Lee KC
- et al.

Lung pathology of fatal severe acute respiratory syndrome.

Lancet. 2003; 361: 1773-1778

- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(615\)](#)
- [Google Scholar](#)

PRCV induces severe lung damage through immune-mediated mechanisms—ie, probably through an increase in the concentrations of proinflammatory cytokines such as TNF α and interleukin 6, whose role in inducing lung damage has been proved using adenoviral vectors in animal models.

[58](#)

- Van Reeth K
- Van Gucht S
- Pensaert M

In vivo studies on cytokine involvement during acute viral respiratory disease of swine: troublesome but rewarding.

Vet Immunol Immunopathol. 2002; 87: 161-168

- [Crossref](#)
- [PubMed](#)
- [Scopus \(79\)](#)
- [Google Scholar](#)

On these grounds, we think that the associations between TNF α and interleukin 6 concentrations and disease severity should also be tested in stored samples from human patients with SARS. If confirmatory results are obtained, then, it would be reasonable to consider chloroquine/hydroxychloroquine to suppress TNF α and interleukin 6 production. For this purpose, efforts to develop an animal model for SARS would be welcome. Such a model would help to clarify the immunemediated component of the symptoms of the disease as well as in testing of chloroquine and other immunomodulatory drugs. These studies could also lay the groundwork for the suggestion that chloroquine be considered for the treatment of other viral infections which involve immunopathology.

Figure thumbnail gr3

Figure 3 Hypothetical model for the potential effects of chloroquine (CQ) on the

immunopathogenesis of severe acute respiratory syndrome (SARS). Proinflammatory cytokines are thought to be important in acute respiratory distress syndrome (ARDS).

[56](#)

- Shanley TP
- Warner RL
- Ward PA

The role of cytokines and adhesion molecules in the development of inflammatory injury.

Mol Med Today. 1995; 1: 40-45

- [Summary](#)
- [Full Text PDF](#)
- [PubMed](#)
- [Scopus \(101\)](#)
- [Google Scholar](#)

We hypothesise that chloroquine (black arrow), by inhibiting TNF α and interleukin 6 (IL6) production, might block the subsequent cascade of events, which leads to ARDS.

- [View Large Image](#)
- [Figure Viewer](#)
- [Download Hi-res image](#)
- [Download \(PPT\)](#)

Conclusions

At present it is difficult to answer the question of whether old chloroquine will be able to live a “second youth”. Due to its main effect—ie, raising endosomal pH—the drug has an exceptionally broad spectrum of antimicrobial activity that could be exploited in many infections. Results obtained in the prophylaxis of Q fever indicate that chloroquine/hydroxychloroquine can be successfully used in the clinical management of infections other than malaria.

[59](#)

- Fenollar F
- Fournier PE
- Carrieri MP
- Habib G
- Messana T
- Raoult D

Risks factors and prevention of Q fever endocarditis.

Clin Infect Dis. 2001; 33: 312-316

- [Crossref](#)
- [PubMed](#)
- [Scopus \(226\)](#)
- [Google Scholar](#)

As regards viral diseases, what is clear is that the drug has antiviral and immunomodulatory effects that warrant particular consideration.

The effects on HIV infection are the best studied among the antiviral effects of chloroquine/hydroxychloroquine and are being tested in clinical trials. The anti-HIV effect of chloroquine/hydroxychloroquine is modest by itself but is, at least in vitro, additive or synergistic when combined with selected antiretrovirals. These in-vitro results warrant in-vivo confirmation in HIV-positive

individuals by comparing the long-term antiviral effect of highly active antiretroviral therapy regimens with and without chloroquine or hydroxychloroquine. If such studies provide encouraging results, they may lead to a strategy whereby co-administration of chloroquine/hydroxychloroquine allows lower doses of antiretrovirals, lessening cost and possibly toxicity. Costlessening would of course be particularly welcome in developing countries. Moreover, the potential ability of chloroquine to inhibit the replication of drug-resistant viral isolates could be important in the treatment of drug-experienced HIV-positive patients who have developed multiple resistance to antiretroviral drugs and thus have limited therapeutic options. In the developing countries where malaria is endemic, the concomitant administration of chloroquine/hydroxychloroquine to a highly active antiretroviral therapy regimen may result (at least where *P falciparum* is still susceptible to chloroquine) in a decreased incidence of malaria episodes that have adverse effects in HIV-infected people, especially during pregnancy.

[60](#)

- Ladner J
- Leroy V
- Karita E
- van de Perre P
- Dabis F

Malaria, HIV and pregnancy.

AIDS. 2003; 17: 275-356

- [Crossref](#)
- [PubMed](#)
- [Scopus \(14\)](#)
- [Google Scholar](#)

Moreover, the anti-inflammatory properties of chloroquine may temper the noxious immune hyperactivation that is characteristic of HIV/AIDS.

[61](#)

- Savarino A
- Bottarel F
- Malavasi F
- Dianzani U

Role of CD38 in HIV-1 infection: an epiphenomenon of T-cell activation or an active player in virus/host interactions?.

AIDS. 2000; 14: 1079-1089

- [Crossref](#)
- [PubMed](#)
- [Scopus \(97\)](#)
- [Google Scholar](#)

Due to its broad spectrum of antiviral activity as well as to its suppressive effects on the production/release of TNF α and interleukin 6, chloroquine/hydroxychloroquine may also find a place in the treatment of other viral infections characterized by symptoms associated with inflammatory processes and/or immune-hyperactivation. We believe that further study should be devoted to the inhibitory effects of chloroquine on the infectivity of flaviviruses, as one of the members of this family, the hepatitis C virus, is of great importance for human pathology and often co-infects individuals with HIV-1. Flaviviridae also include several arthropod-borne viruses such as the yellow fever virus and the West Nile virus, which has recently caused an epidemic in North America.

Finally, we want to share with the scientific community the speculative hypothesis that chloroquine/hydroxychloroquine, due to its antiviral and anti-inflammatory properties, may have some

effect on SARS. We emphasise the need of testing in cell cultures infected with SARS coronavirus the effects of chloroquine, as well as those of other substances possessing in-vitro activity against members of the coronaviridae family. We should remember that the possibility of new outbreaks of SARS cannot be excluded. In the absence of effective inhibitors of SARS coronavirus, the possibility of an inhibition, at least in vitro, of the replication of this virus would represent a breakthrough in the knowledge of SARS.

Search strategy and selection criteria

We did literature reviews using relevant Medline search terms, in various combinations—“chloroquine”, “virus”, “retrovirus”, “TNF α ”, “cytokines”, “endothelium”, “macrophages”, “HIV” “SARS”, “NF-kappa B”, “coronavirus”, “proinflammatory cytokines”, and “ARDS”—screened articles for relevance, and reviewed references. Because of space restrictions we (1) cited review articles in place of original manuscripts where possible, (2) excluded those articles whose content was not in line with the bulk of the published information without giving convincing explanations, and (3) ranked the articles on the basis of relevance, date of publication, and journal impact factor. We also searched the internet for relevant web pages, discarded those edited by people/institutions not directly involved in research, and reviewed references. References are not intended to provide a comprehensive listing, but were chosen to best highlight the critical issues.

Conflicts of interest

We have no conflicts of interest.

Acknowledgments

We are grateful to Special Project AIDS, Istituto Superiore di Sanita, Rome, Italy, for financial support.

References

1. 1.
 - Canadian rheumatology association
Canadian Consensus Conference on hydroxychloroquine.
J Rheumatol. 2000; 27: 2919-2921
[View in Article](#)
 - [PubMed](#)
 - [Google Scholar](#)
2. 2.
 - Savarino A
 - Gennero L
 - Sperber K
 - Boelaert JR

The anti-HIV-1 activity of chloroquine.
J Clin Virol. 2001; 20: 131-135
[View in Article](#)
 - [Scopus \(74\)](#)
 - [PubMed](#)
 - [Summary](#)
 - [Full Text](#)
 - [Full Text PDF](#)
 - [Google Scholar](#)
3. 3.
 - Boelaert JR
 - Piette J
 - Sperber K

The potential place of chloroquine in the treatment of HIV-1–infected patients.
J Clin Virol. 2001; 20: 137-140
[View in Article](#)

- [Scopus \(43\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

4. 4.

- Ohkuma S
- Poole B

Cytoplasmic vacuolation of mouse peritoneal macrophages and the uptake into lysosomes of weakly basic substances.

J Cell Biol. 1981; 90: 656-664

[View in Article](#)

- [Scopus \(308\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

5. 5.

- Pescarmona GP
- Morra E
- Aldieri E
- Ghigo D
- Bosia A

Movements of vesicles in eukaryotic cells: role of intravesicle protons as a fuel and modulation of their concentration by drugs or metabolic changes.

MRS Bull. 1998; 489: 212-217

[View in Article](#)

- [Google Scholar](#)

6. 6.

- Vezmar M
- Georges E

Reversal of MRP-mediated doxorubicin resistance with quinoline-based drugs.

Biochem Pharmacol. 2000; 59: 1245-1252

[View in Article](#)

- [Scopus \(74\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

7. 7.

- Vezmar M
- Georges E

Direct binding of chloroquine to the multidrug resistance protein (MRP): possible role for MRP in chloroquine drug transport and resistance in tumor cells.

Biochem Pharmacol. 1998; 56: 733-742

[View in Article](#)

- [Scopus \(54\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

8. 8.

- Byrd TF
- Horwitz MA

Chloroquine inhibits the intracellular multiplication of *Legionella pneumophila* by limiting the availability of iron. A potential new mechanism for the therapeutic effect of chloroquine against

intracellular pathogens.

J Clin Invest. 1991; 88: 351-357

[View in Article](#)

- [Scopus \(100\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

9. 9.

- Legssyer R
- Josse C
- Piette J
- Ward RJ
- Crichton RR

Changes in function of iron-loaded alveolar macrophages after in vivo administration of desferrioxamine and/or chloroquine.

J Inorg Biochem. 2003; 94: 36-42

[View in Article](#)

- [Scopus \(20\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

10. 10.

- Gonzalez-Dunia D
- Cubitt B
- de la Torre JC

Mechanism of Borna disease virus entry into cells.

J Virol. 1998; 72: 783-788

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

11. 11.

- Ros C
- Burckhardt CJ
- Kempf C

Cytoplasmic trafficking of minute virus of mice: low-pH requirement, routing to late endosomes, and proteasome interaction.

J Virol. 2002; 76: 12634-12645

[View in Article](#)

- [Scopus \(62\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

12. 12.

- Diaz-Griffero F
- Hoschander SA
- Brojatsch J

Endocytosis is a critical step in entry of subgroup B avian leukosis viruses.

J Virol. 2000; 76: 12866-12876

[View in Article](#)

- [Scopus \(59\)](#)
- [Crossref](#)
- [Google Scholar](#)

13. 13.

- Bishop NE

Examination of potential inhibitors of hepatitis A virus uncoating.

Intervirology. 1998; 41: 261-271

[View in Article](#)

- [Scopus \(35\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

14. 14.

- Ferreira DF
- Santo MP
- Rebello MA
- Rebello MC

Weak bases affect late stages of Mayaro virus replication cycle in vertebrate cells.

J Med Microbiol. 2000; 49: 313-318

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

15. 15.

- Harley CA
- Dasgupta A
- Wilson DW

Characterization of herpes simplex virus-containing organelles by subcellular fractionation: role for organelle acidification in assembly of infectious particles.

J Virol. 2001; 75: 1236-1251

[View in Article](#)

- [Scopus \(107\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

16. 16.

- Randolph VB
- Winkler G
- Stollar V

Acidotropic amines inhibit proteolytic processing of flavivirus prM protein.

Virology. 1990; 174: 450-458

[View in Article](#)

- [Scopus \(125\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

17. 17.

- Tsai WP
- Nara PL
- Kung HF
- Oroszlan S

Inhibition of human immunodeficiency virus infectivity by chloroquine.

AIDS Res Hum Retroviruses. 1990; 6: 481-489

[View in Article](#)

- [Scopus \(93\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

18. 18.

- Baughman RP

- Lower EE
- du Bois RM

Sarcoidosis.

Lancet. 2003; 361: 1111-1118

[View in Article](#)

- [Scopus \(558\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

19. 19.

- Jeong J-Y
- Jue D-M

Chloroquine inhibits processing of tumor necrosis factor in lipopolysaccharidestimulated RAW 264·7 macrophages.

J Immunol. 1997; 158: 4901-4907

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

20. 20.

- Bondeson J
- Sundler R

Antimalarial drugs inhibit phospholipase A2 activation and induction of interleukin β and tumor necrosis factor α in macrophages.

General Pharmacol. 1998; 30: 357-366

[View in Article](#)

- [Scopus \(48\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

21. 21.

- Van den Borne BE
- Dijkmans BA
- de Rooij HH
- le Cessie S
- Verweij CL

Chloroquine and hydroxychloroquine equally affect tumor necrosis factor- α , interleukin 6 and interferon- γ production by peripheral blood mononuclear cells.

J Rheumatol. 1997; 24: 55-60

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

22. 22.

- Karres I
- Kremer J-P
- Dietl I
- Steckholzer U
- Jochum M
- Ertel W

Chloroquine inhibits proinflammatory cytokine release into human whole blood.

Am J Physiol. 1998; 274: R1058-R1064

[View in Article](#)

- [PubMed](#)

23. 23. [Google Scholar](#)

- Picot S
- Peyron F
- Donadille A
- Vuillez J-P
- Barbe G
- Ambroise-Thomas P

Chloroquine-induced inhibition of the production of TNF, but not of IL-6, is affected by disruption of iron metabolism.

Immunology. 1993; 80: 127-133

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

24. 24.

- Weber SM
- Levitz SM

Chloroquine interferes with lipopolysaccharide-induced TNF- α gene expression by a nonlysosomotropic mechanism.

J Immunol. 2000; 165: 1534-1540

[View in Article](#)

- [Scopus \(109\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

25. 25.

- Jeong J-Y
- Choi JW
- Jeon K-I
- Jue D-M

Chloroquine decreases cell-surface expression of tumour necrosis factor receptors in human histiocytic U-937 cells.

Immunol. 2002; 105: 83-91

[View in Article](#)

- [Scopus \(26\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

26. 26.

- Nooteboom A
- Hendriks T
- Otteholler I
- van der Linden CJ

Permeability characteristics of human endothelial monolayers seeded on different extracellular matrix proteins.

Mediators Inflamm. 2000; 9: 235-241

[View in Article](#)

- [Scopus \(33\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

27. 27.

- Bernstein HN

Ocular safety of hydroxychloroquine.

Ann Ophthalmol. 1991; 23: 292-296

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

28. 28.

- Bernstein HN

Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy.

Am J Med. 1983; 75: 25-34

[View in Article](#)

- [Scopus \(104\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text PDF](#)
- [Google Scholar](#)

29. 29.

- Herman K
- Leys A
- Spileers W

(Hydroxy)-chloroquine retinal toxicity: two case reports and safety guidelines.

Bull Soc Belge Ophtalmol. 2002; 284: 21-29

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

30. 30.

- Klinger G
- Morad Y
- Westall CA
- et al.

Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases.

Lancet. 2001; 358: 813-814

[View in Article](#)

- [Scopus \(94\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

31. 31.

- Sperber K
- Kalb TH
- Stecher VJ
- Banerjee R
- Mayer L

Inhibition of human immunodeficiency virus type 1 replication by hydroxychloroquine in T cells and monocytes.

AIDS Res Hum Retroviruses. 1993; 9: 91-98

[View in Article](#)

- [Scopus \(100\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

32. 32.

- Pardridge WM

- Yang J
- Diagne A

Chloroquine inhibits HIV-1 replication in human peripheral blood lymphocytes.

Immunol Lett. 1998; 64: 45-47

[View in Article](#)

- [Scopus \(24\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

33. 33.

- Savarino A
- Gennero L
- Chen HC
- et al.

Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity.

AIDS. 2001; 15: 2221-2229

[View in Article](#)

- [Scopus \(93\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

34. 34.

- Sperber K
- Louie M
- Kraus T
- et al.

Hydroxychloroquine treatment of patients with human immunodeficiency virus type 1.

Clin Ther. 1995; 17: 622-636

[View in Article](#)

- [Scopus \(101\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text PDF](#)
- [Google Scholar](#)

35. 35.

- Sperber K
- Chiang G
- Chen H
- et al.

Comparison of hydroxychloroquine with zidovudine in asymptomatic patients infected with HIV-1.

Clin Ther. 1997; 19: 913-923

[View in Article](#)

- [Scopus \(74\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text PDF](#)
- [Google Scholar](#)

36. 36.

Debiaggi M, Bruno R, Sacchi P, Filice G. Antiviral activity of chloroquine against HIV-1 strains resistant to antiretroviral drugs. *Antiviral Res* (in press)

[View in Article](#)

- [Google Scholar](#)

37. 37.

- Chiang G
- Sassaroli M
- Louie M
- Chen H
- Stecher VJ
- Sperber K

Inhibition of HIV-1 replication by hydroxychloroquine: mechanism of action and comparison with zidovudine.

Clin Ther. 1996; 18: 1080-1092

[View in Article](#)

- [Scopus \(65\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text PDF](#)
- [Google Scholar](#)

38. 38.

- Boelaert JR and Sperber K

Antiretroviral therapy.

Lancet. 1998; 352: 1224-1225

[View in Article](#)

- [Scopus \(11\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

39. 39.

- Boelaert JR
- Sperber K
- Piette J

Chloroquine exerts an additive in vitro anti-HIV-1 effect, when combined to zidovudine and hydroxyurea.

Biochem Pharmacol. 2001; 61: 1531-1535

[View in Article](#)

- [Scopus \(18\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

40. 40.

- Paton NI
- Aboulhab J
- Karim F

Hydroxychloroquine, hydroxycarbamide, and didanosine as economic treatment for HIV-1.

Lancet. 2002; 359: 1667-1668

[View in Article](#)

- [Scopus \(40\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

41. 41.

- Boelaert JR
- Dom GM

- Huitema AD
- Beijnen JH
- Lange JM

The boosting of didanosine by allopurinol permits a halving of the didanosine dosage.

AIDS. 2002; 16: 2221-2223

[View in Article](#)

- [Scopus \(10\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

42. 42.

- Mofenson LM
- McIntyre JA

Advances and research directions in the prevention of mother-to-child HIV-1 transmission.

Lancet. 2000; 355: 2237-2244

[View in Article](#)

- [Scopus \(168\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

43. 43.

- Boelaert JR
- Yaro S
- Augustijns P
- et al.

Chloroquine accumulates in breast milk cells. Potential impact as adjuvant to antiretroviral prophylaxis for postnatal mother-to-child transmission of HIV-1.

AIDS. 2001; 15: 2205-2206

[View in Article](#)

- [Scopus \(25\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

44. 44.

- DeCock KM
- Fowler MG
- Mercier E
- et al.

Prevention of mother-to-child transmission of HIV-1 in resource-poor countries: translating research into policy and practice.

JAMA. 2000; 283: 1175-1182

[View in Article](#)

- [Scopus \(731\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

45. 45.

- Corbett EL
- Steketee RW
- ter Kuile FO
- Latif AS
- Kamali A

- Hayes RJ

HIV-1/AIDS and the control of other infectious diseases in Africa.

Lancet. 2002; 359: 2177-2187

[View in Article](#)

- [Scopus \(169\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

46. 46.

- Clerici M
- Butto S
- Lukwiya M
- et al.

Immune activation in Africa is environmentally driven and is associated with upregulation of CCR5.

AIDS. 2000; 14: 2083-2092

[View in Article](#)

- [Scopus \(107\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

47. 47.

- Bentwich Z
- Maartens G
- Torten D
- Lal AA
- Lal RB

Concurrent infections and HIV pathogenesis.

AIDS. 2000; 14: 2071-2081

[View in Article](#)

- [Scopus \(108\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

48. 48.

- Montano MA
- Nixon CP
- Ndung'u T
- et al.

Elevated tumor necrosis factor- α activation of human immunodeficiency virus subtype 1 in southern Africa is associated with an NF- κ B enhancer gain-of-function.

J Infect Dis. 2000; 181: 76-81

[View in Article](#)

- [Scopus \(79\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

49. 49.

- Poutanen SM
- Low DE
- Henry B
- et al.

Identification of severe acute respiratory syndrome in Canada.

N Engl J Med. 2003; 348: 1995-2005

[View in Article](#)

- [Scopus \(902\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

50. 50.

- So LK
- Lau AC
- Yam LY
- et al.

Development of a standard treatment protocol for severe acute respiratory syndrome.

Lancet. 2003; 361: 1615-1617

[View in Article](#)

- [Scopus \(258\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

51. 51.

- Peiris JS
- Lai ST
- Poon LL
- et al.

Coronavirus as a possible cause of severe acute respiratory syndrome.

Lancet. 2003; 361: 1319-1325

[View in Article](#)

- [Scopus \(1871\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

52. 52.

- Drosten C
- Gunther S
- Preiser W
- et al.

Identification of a novel coronavirus in patients with severe acute respiratory syndrome.

N Engl J Med. 2003; 348: 1967-1976

[View in Article](#)

- [Scopus \(2417\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

53. 53.

- Blau D
- Holmes K

Human Coronavirus HCoV-229E enters susceptible cells via the endocytic pathway.

in: Lavi E *The Nidoviruses, Coronaviruses and Arteriviruses.* Kluwer, New York 2001: 193-197

[View in Article](#)

- [Google Scholar](#)

54. 54.

- Nauwynck HJ
- Duan X
- Favoreel HW
- Van Oostveldt P
- Pensaert MB

Entry of porcine reproductive and respiratory syndrome virus into porcine alveolar macrophages via receptor-mediated endocytosis.

J Gen Virol. 1999; 80: 297-305

[View in Article](#)

- [PubMed](#)
- [Google Scholar](#)

55. 55.

- Peiris JS
- Chu CM
- Cheng VC
- et al.

Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study.

Lancet. 2003; 361: 1767-1772

[View in Article](#)

- [Scopus \(1318\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

56. 56.

- Shanley TP
- Warner RL
- Ward PA

The role of cytokines and adhesion molecules in the development of inflammatory injury.

Mol Med Today. 1995; 1: 40-45

[View in Article](#)

- [Scopus \(101\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text PDF](#)
- [Google Scholar](#)

57. 57.

- Nicholls JM
- Poon LL
- Lee KC
- et al.

Lung pathology of fatal severe acute respiratory syndrome.

Lancet. 2003; 361: 1773-1778

[View in Article](#)

- [Scopus \(615\)](#)
- [PubMed](#)
- [Summary](#)
- [Full Text](#)
- [Full Text PDF](#)
- [Google Scholar](#)

58. 58.

- Van Reeth K

- Van Gucht S
- Pensaert M

In vivo studies on cytokine involvement during acute viral respiratory disease of swine: troublesome but rewarding.

Vet Immunol Immunopathol. 2002; 87: 161-168

[View in Article](#)

- [Scopus \(79\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

59. 59.

- Fenollar F
- Fournier PE
- Carrieri MP
- Habib G
- Messana T
- Raoult D

Risks factors and prevention of Q fever endocarditis.

Clin Infect Dis. 2001; 33: 312-316

[View in Article](#)

- [Scopus \(226\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

60. 60.

- Ladner J
- Leroy V
- Karita E
- van de Perre P
- Dabis F

Malaria, HIV and pregnancy.

AIDS. 2003; 17: 275-356

[View in Article](#)

- [Scopus \(14\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

61. 61.

- Savarino A
- Bottarel F
- Malavasi F
- Dianzani U

Role of CD38 in HIV-1 infection: an epiphenomenon of T-cell activation or an active player in virus/host interactions?.

AIDS. 2000; 14: 1079-1089

[View in Article](#)

- [Scopus \(97\)](#)
- [PubMed](#)
- [Crossref](#)
- [Google Scholar](#)

Article Info

Publication History

Published: November 2003

Identification

DOI: [https://doi.org/10.1016/S1473-3099\(03\)00806-5](https://doi.org/10.1016/S1473-3099(03)00806-5)

Copyright

© 2003 Elsevier Ltd. All rights reserved.

ScienceDirect

[Access this article on ScienceDirect](#)

[Hide Caption](#)[Download](#)[See figure in article](#)

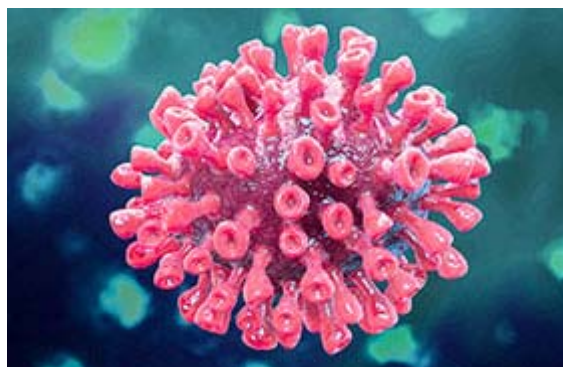
[Toggle Thumbstrip](#)

- [View Large Image](#)
- [Download Hi-res image](#)
- [Download .PPT](#)

Linked Articles

- [Chloroquine or hydroxychloroquine for prophylaxis of COVID-19](#)
 - [Full-Text](#)
 - [PDF](#)

Related Hub



[COVID-19 Resource Centre](#)

Access the latest 2019 novel coronavirus disease (COVID-19) content from across *The Lancet* journals as it is published.

[Hide Caption](#)[Download](#)[See figure in Article](#)

[Toggle Thumbstrip](#)

- [Download Hi-res image](#)
- [Download .PPT](#)

THE LANCET

•